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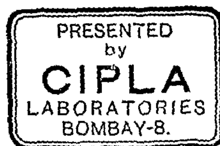
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Modern Treatment

A GUIDE
FOR GENERAL PRACTICE

by fifty-three authors



edited by

AUSTIN SMITH, M.D.

Editor of the Journal of the American Medical Association

and

PAUL L. WERMER, M.D.

Secretary, Committee on Research, American Medical Association

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CONTRIBUTORS

GEORGE J ANDROS M D
Assistant Professor of Obstetrics and Gynecology, University of Chicago School of Medicine, Chicago Illinois

E. B ASTWOOD M D
Professor of Medicine, Tufts College Medical School, Boston, Massachusetts

RUSSELL S BOLES, M D
Associate Professor of Medicine, Graduate School of Medicine University of Pennsylvania, Philadelphia, Pennsylvania

EDWARD L. BORTZ, M D
Associate Professor of Medicine Jefferson Medical College and Graduate School University of Pennsylvania, Philadelphia, Pennsylvania

ADRIAN BRODEY, M D
Lecturer Department of Dermatology and Syphilology New York Polyclinic Medical School and Hospital, New York

W J R CAMP, M D
Professor of Pharmacology and Toxicology and State Toxicologist, University of Illinois College of Medicine Division of Toxicology Chicago, Illinois

J W J CARPENDER M D
Associate Professor of Radiology and Director of Radiation Therapy University of Chicago School of Medicine, Chicago, Illinois

SIDNEY CARTER, M D
Assistant Professor in Neurology Columbia University College of Physicians and Surgeons, New York

ANTHONY C CIPOLLARO, M D
Professor and Director of the Department of Dermatology and Syphilology New York Polyclinic Medical School and Hospital, New York

BERNARD CONLEY M S
Secretary Committee on Pesticides American Medical Association

M EDWARD DAVIS, M D
Joseph Bolivar De Lee Professor of Obstetrics and Gynecology, University of Chicago School of Medicine, Chicago Illinois

ARTHUR C. DeGRAFF, M D
Professor of Therapeutics New York University College of Medicine New York

ERNEST CARROLL FAUST, PH D
William Vincent Professor of Tropical Diseases and Hygiene Department of Tropical Medicine and Public Health, Tulane University New Orleans Louisiana

CONTRIBUTORS

SAMUEL M FEINBERG M D
Professor of Medicine Chief of the Allergy Clinic and Director of Allergy Research Laboratory Northwestern University Medical School Chicago Illinois

S CHARLES FREED M D
Adjunct in the Department of Medicine and Research Associate at the Harold Brunn Institute Mount Zion Hospital San Francisco California

JOSEPH T FREEMAN M D
Associate in Medicine and Special Lecturer in Geriatrics Woman s Medical College of Philadelphia and the Graduate School University of Pennsylvania Medical School Philadelphia Pennsylvania

GRACE A GOLDSMITH M D
Professor of Medicine Tulane University School of Medicine New Orleans Louisiana

KEITH S GRIMSON M D
Professor of Surgery Duke University School of Medicine Duke Hospital Durham North Carolina

RICHARD D HAHN M D
Assistant Professor of Medicine Johns Hopkins School of Medicine Baltimore Maryland

ROBERT C HARDIN M D
Associate Professor of Internal Medicine College of Medicine State University of Iowa Iowa City Iowa

GEORGE T HARRELL M D
Professor of Internal Medicine Bowman Gray School of Medicine Wake Forest College Winston Salem North Carolina

JAMES PAISLEY HENDRIX M D
Associate Professor of Medicine and Therapeutics Duke University School of Medicine Durham North Carolina

H CORWIN HINSHAW M D
Clinical Professor of Medicine and Chief Division of Diseases of the Chest Stanford University School of Medicine San Francisco California

JAY J JACOBY PH D M D
Professor and Director Department of Anesthesia Ohio State University Columbus Ohio

CHESTER S KEEFER M D
Wade Professor of Medicine Boston University School of Medicine Boston Massachusetts

† ROY R KRACKE M D
Dean and Professor of Clinical Medicine Medical College of Alabama University of Alabama Birmingham Alabama

EDWARD M KRUSEN JR M D
Assistant Professor and Chairman of the Department of Physical Medicine and Rehabilitation Southwestern Medical College of the University of Texas Houston Texas

FRANK H KRUSEN M D
Professor of Physical Medicine Mayo Foundation University of Minnesota Rochester Minnesota

† Deceased

CONTRIBUTORS

CHAUNCEY D LEAKE PH D
Vice Pres dent Univers ty of Texas Med cal Branch Galveston Texas

FRANCIS L LEDERER M D
Professor and Head of the Department Departn ent of Otolaryngology Univers ty of Ill nois College of Med c ne Ch cago Ill no s

JOHN A LUETSCHER JR M D
Assoc ate Professor of Med c ne Stanford Un ers ty School of Med cine San Franc sco Californ a

WILLIAM A MANN M D
Professor of Ophthalmology Northwestern Un vers ty Med cal School Ch cago Ill no s

RICHARD E MARCUS M D
Ass stant Professor of Otolaryngology Un vers ty of Ill nois College of Med c ne Ch cago Ill no s

CHARLES D MARPLE M D
Med cal D rector Amer can Heart Associat on

H HOUSTON MERRITT M D
Professor of Neurology College of Phys c ans and Surgeons Colu nb a Un vers ty New York

JOSEPH EARLE MOORE M D
Associate Professor of Med c ne Jol ns Hopk ns Un ers ty Balt more Maryland

RUSSELL L NICHOLS M D
Radiologist Thomas D Lee Memor al Hosp tal Ogden Utah

IRVINE H PAGE M D
D rector of Research Cleveland Cl n c Foundat on Cleveland Oh o

HAROLD E PEARSON M D
Professor of Publ c Health Un vers ty of Southern Cal forn a School of Med c ne Los Angeles Californ a

CARL C PFEIFFER PH D M D
Professor and Head of the Department Department of Pharmacology Un vers ty of Ill no s College of Med c ne Ch cago Ill no s

ISRAEL I RITTER M D
Cl n cal Ass stant Profe sor of Me l c ne Un vers ty of Ill no s Ch cago Illino s

† EMANUEL B SCHOENBACH M D
Professor of Med c ne State Un vers ty of New York College of Med c ne New York

STEVEN O SCHWARTZ M D
Professor of Hematology Ch cago Med cal Scl ool Ch cago Ill no s

AUSTIN SMITH M D
Ed tor *The Journal of the Ame ca Med cal A oc at on* and Ed or n Ch ef of A M A Sc ent fic Publ cat ons Formerly Secretary of he Counc l on Pharmacy and Cl em stry of the Amer can Med cal As oc at on

IRVING E STECK M D
Cl n cal Ass stant Professor of Med cine Un vers ty of Ill no s College of Med c ne Ch cago Ill no s

BERNARD STRAUS M D
Ch ef of the Med cal Serv ce Veterans Adm n strat on Hosp tal Bronx New York

† De eased

CONTRIBUTORS

ROBERT D TAYLOR, M D
Staff Member Research Division Cleveland Clinic, Cleveland Ohio

W P VANDER LAAN, M.D
Assistant Professor of Medicine, Tufts College Medical School, Boston, Massachusetts

LOUIS WEINSTEIN, M D
Associate Professor of Medicine Boston University School of Medicine, Boston, Massachusetts

EDWARD WEISS, M D
Professor of Clinical Medicine Temple University School of Medicine, Philadelphia Pennsylvania

PAUL L. WERMER, M D
Secretary, Committee on Research of the Council on Pharmacy and Chemistry, American Medical Association Chicago Illinois

SIDNEY C WERNER, M D
Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons New York

IRVING S WRIGHT, M D
Professor of Clinical Medicine Cornell University Medical College, New York

PREFACE

THE practice of medicine is a bedside occupation guided largely by experience However the general practitioner today is confronted with many more treatments than he can assess successfully from his own practice While a book cannot be substituted for bedside observation the experience of other practitioners translated into the written word may often be helpful This is especially true if the contributors confine their practice to specialized subjects in a way which permits them to evaluate and select the most practical and effective of alternative therapeutic proposals on the basis of a concentrated experience

This book is designed to provide the general practitioner with a useful and authoritative guide to the clinical problems in therapy which he is likely to encounter A group of postgraduate teachers have joined in creating a volume which presents the practical essentials of today s therapy In each discussion attention is focused on the most effective treatment for the condition in the judgment of the author of the section However the descriptions are not limited to his preferences Where appropriate alternative forms of treatment are also considered along with the author s evaluation of their role in the physician s armamentarium It is recognized that often the recommended treatment may require supportive measures or may not be feasible under particular circumstances or may even be contraindicated by some supervening complication Often the rationale of therapy must be understood to apply it properly The authors attempt to take account of all such factors and provide sufficient information to enable the practitioner to adapt the best available treatment to the needs of each individual patient

The chapters have been organized to present the information in a logical sequence as the clinical problem confronts the practitioner Each chapter is intended to be sufficiently complete to stand by itself Occasionally a subject may be mentioned of necessity in more than one chapter

Some material not exclusively treatment is included because of its important influence on the selection and continuation of therapy The decision as to which are the important diseases the amount of space to be devoted to

the disease and the necessity for brief discussion of etiology, pathology, and signs and symptoms was decided to a large extent on the basis of appraisals provided by the contributors. The physical limitations of a single volume imposed certain restrictions on contents, but the more grave or difficult diseases to treat have been given the space required for a clear and usable discussion. The diseases included here are those commonly encountered in this country by the general practitioner. In some instances more exotic diseases are taken up because world travel and military commitments today increase the likelihood of their occurrence in this country. There are also a few commonly encountered conditions, such as alcoholism or drug addiction, which have been omitted deliberately because at this time it is believed that much more experience is needed to permit satisfactory evaluation of therapeutic and social measures now under investigation.

Certain chapters are included which might not ordinarily be expected in this type of book. The aim was to put between the covers of a single book as much as possible of the information required to carry out therapy in general practice intelligently and successfully. Therefore, it seemed clinically valuable to incorporate discussions of causes of individual variation in response of patients to disease, drugs, physical and toxic agents. Recognition also had to be accorded the diagnostic tests and technics which direct and influence the treatment. And there are certain special therapeutic aids which can be readily employed by the general practitioner but which require separate discussions to present sufficient guidance in their use to be of practical value. Therefore, chapters are devoted to such topics as the principles of pharmacology, immunity, radiology, diagnostic laboratory procedures, surgery, inhalation therapy, and physical medicine. The importance of some subjects, for example, the antimicrobial agents, required meticulous analysis in specially prepared chapters. Likewise note has been taken of the increasing age of our population and of the special problems involved in the psychosomatic ills of mankind.

Underlying the whole book is the principle that therapy involves much more than the simple prescription of medicaments. The patient, from the time he walks in the office door until he is discharged, must be regarded as a person with a complaint or a disease and not as a piece of isolated diseased tissue which is capable of locomotion. If the practitioner has an appreciation of the treatment of the whole person, he can apply the necessary therapy regardless of the site or the extent of the disease. Treatment of disease cannot be mechanical or distant; it must be personal and objective. It rests on many factors, but the most important aspect is judgment which rests on knowledge.

Modern Treatment is the culmination of several years of effort to provide

a new kind of aid for general practice, an aid which is sorely needed in this day of breath taking progress Our grateful thanks go to the eminent contributors whose patient cooperation has made the book possible

The editors would like to express their appreciation of the helpful comments that have been provided by George Hall and Frederick Steigmann They also would like to express their appreciation of the assistance that has been offered in the preparation of the manuscript by Alice Molander, Margaret Barr, and Blanche Marston

AUSTIN SMITH, M D
PAUL L WERMER, M D

1. The Patient-Physician Relationship

AUSTIN SMITH
& PAUL L. WERMER

WHEN a subject is reviewed comprehensively by a group of collaborating authors it is generally necessary to provide, as an orientation, a discussion of some common, unifying factors This is the objective of the present chapter Some of the principles and recommendations may be considered elementary by many readers but they warrant emphasis because they are both important and often overlooked

Essentials of Diagnosis

TREATMENT depends on correct diagnosis Diagnosis, in turn, depends on the patient's cooperation the clinical history, and the physical and laboratory examination These elements are of prime importance in a rational approach to therapeutics and serve as a logical starting point for a general discussion of the subject

THE PATIENT'S COOPERATION

The patient s cooperation is one of those intangible factors which because of the current sophistication and dependence on mechanical devices and on laboratory technics, is too often overlooked as a factor in both diagnosis and therapy Unless carefully developed, the relation of patient and physician can degenerate into an impersonal and often mutually unsatisfactory series of encounters Hence, if the cooperation of the patient is lacking, the physician must actively seek it The physician should realize that his relationship with a patient is an intimate experience in which the life, happiness, and livelihood of the latter often are involved To this situation, both the interviewer and the interviewed bring their contribution of personality traits and education They bring their experiences, their failings, their prejudices, and even folklore, thus limiting their capacity for mutual understanding and trust Yet success in diag

nosis and in treatment depends on the patient's unqualified cooperation in securing an accurate history and in faithfully observing regimens of treatment To secure this cooperation the physician should consciously adapt his approach and behavior to each patient's needs and personality He should adopt and vigilantly maintain throughout his years of practice a code of behavior and an attitude which create and uphold his reputation for integrity and human understanding There is nothing new in this concept for these basic tenets of medical behavior are contained in the Aesculapian oath

Just as each physician differs in the sum of his knowledge his adeptness and insight so does each patient differ in symptoms signs and responses—and not to be forgotten his ability to describe them These factors and their permutations make it necessary for the physician to consider the patient as a whole and consider the illness as a part of the whole Balanced against the patient's needs are the physician's capabilities and limitations The physician should recognize his own abilities and apply them to their fullest extent Inevitably by following this discipline of mind and behavior he will gain the trust and cooperation of the patient

During his initial visit, the patient gains his first impression of the physician even before meeting him through the appearance of his waiting room The need for cleanliness orderliness a pleasing restful atmosphere current reputable magazines sufficient seating accommodations and above all a pleasant tactful receptionist cannot be overemphasized This office assistant receptionist nurse technician or secretary whatever she may be called can do either much good or harm She usually makes the appointment, greets the patient and secures preliminary information She escorts the visitor to the examining or consultant room helps undress the female patient, and holds the young patient She may draw blood for laboratory study or do other things that bring her into intimate contact with the patient Pleasant personality, poise good grooming and character, judgment truthfulness tact initiative and attentiveness are the qualities that should be sought for and cultivated in an office assistant

Just as the physician respects medical ethics so must he teach his office assistant the importance of observing them Perhaps the physician should insist that she read his copy of *Principles of Medical Ethics* which can always be obtained from the headquarters office of the American Medical Association or through his local or state medical society He might also require her to become familiar with the organization of county state and national medical societies and institutions and some of the less understood activities of everyday medical practice for example patient physician relations and the meaning of privileged communications This may prevent criticism or even lawsuits caused by careless talk by office personnel

One of the most irritating habits of office assistants is their refusal to greet new arrivals until the patient musters up enough courage to ask for information A word of welcome to the entering patient goes a long way toward placing the patient at ease and in contenting him if he has to wait longer than he expected to see the physician The word of welcome is something that physicians also can practice, for gruffness or brusqueness may be misinterpreted as lack of interest The office assistant and physician should be aware of their complementary roles in influencing the patient and in putting him and especially her at ease

THE CLINICAL HISTORY

After the patient is at ease the clinical history, or case taking becomes the next problem It is not possible to obtain a completely satisfactory history and a revealing

physical examination unless the patient cooperates To gain this cooperation the physician must be tactful sympathetic and friendly but should not be forward He must be confident without appearing too self assured He must recognize that old people and sick people tire easily Brusqueness on the part of the physician failure to keep his appointments on time his criticism of others an air of offhandedness and a disrespect for the religious beliefs of patients often damage the reputation of the otherwise competent physician Except in emergencies the clinical history should normally precede the physical examination but there are times when this is not possible At other times it is amplified as the physical examination proceeds One should not be led astray by needless detail however The primary reason for interrogating the patient is to elicit information concerning his present health his past illnesses the status and health of his family and any other factors that might have a bearing on his present illness such as the happiness of his family and contentment with his employment Proper questioning also can lead to the discovery of other unsuspected illness The history must not be taken hurriedly the patient should be allowed to tell his story in his own words whenever possible The examiner should avoid asking leading questions except when he uses them deliberately as for example when he suspects malingering and seeks contradictions He should not ask the same question repeatedly unless he carefully rephrases it as the patient may attach undue significance to it or may accuse the examiner of not listening to his answers

The physician seldom if ever fails to secure answers to such important questions as Of what do you complain? or How long have the symptoms been present? What he may neglect are those queries relating to occupation surroundings habits exercise hobbies foods and travel which have a less direct bearing on the disease Of equal importance are questions concerning sores rashes sore throat gastrointestinal and visual disturbances for these may be as informative as learning whether or not the present illness appeared suddenly or gradually It is also necessary to know whether or not the patient has been receiving treatment elsewhere If questioning discloses for example that the patient has taken thyroid medication his complaint of nervousness irritability, and loss of weight may be explained If the patient reports that he has been using phenobarbital for hypertension he may reveal the cause of a mysterious' skin disorder Or if a female patient says that she has been dosing herself with aspirin the cause of uterine bleeding may become apparent Even religious background may be helpful because one sect avoids pork another avoids all meat Such information may permit the examiner to exclude certain diagnostic presumptions

Sometimes it is difficult to reconcile the mildness of complaints with the severity of the disease or its location Careful but when necessary pointed questioning may reveal the patient has been resorting to self medication for even long periods and may be presenting himself while under the influence of some discomfort relieving remedy In such a situation it is impossible to obtain the true picture without proper questioning The results of the physical examination alone could be misleading

The accuracy of the history is limited by the patient's ability to express himself and to understand the questions of the physician Occasionally language difficulties differences in interpretation of common words and phrases and mental development may provide handicaps The very young cannot speak for themselves and the very old may not think clearly or may become less articulate as age advances In addition some people try to determine their own diagnosis and hence deliberately or unconsciously

shape their comments to favor their beliefs Finally, but not of least importance, is the influence that the mind has on the body which may cause signs of physical illness and which may interfere with the expected response to treatment Psychosomatic medicine has become a term of real medical significance

When a patient goes to a physician he may complain about an ailment whose cause is immediately apparent On the other hand, the symptoms may be so indefinite that a diagnosis is difficult to obtain In still other instances a sign or a symptom may cause a person to seek medical aid, but a thorough examination will uncover a far more serious, previously unapparent illness Frequently, illness is discovered by chance This observation is particularly suited to the detection of cancer, tuberculosis, and other insidious diseases For example, lesions of the lung and diabetes are often discovered incidentally as the examiner is seeking data on other diseases

THE EXAMINATION

Since the art of therapy depends on accurate diagnosis, the examining physician must look, listen, and touch He must repeat these procedures until he is thoroughly satisfied with the results of his physical examination otherwise, physical diagnosis becomes a shallow pretense If ever the examiner uses all his senses and calls on all his experience, it is when he is undertaking this phase of diagnosis He must be highly critical and not undertake a merely routine examination He must deviate from routine in order to use fully the diagnostic possibilities of listening looking, and feeling But when he listens, he must hear when he looks he must see when he feels he must sense

While examining the patient, the examiner should pass critically from one part of the body to another in an orderly, progressive manner He should always feel as if he were looking for an excuse to pause and study in more detail He should not neglect the body orifices and sense organs He should undertake percussion, palpation, and auscultation with a determination to be thorough He should note the positions and actions of the patient as they may facilitate a diagnosis Drawn up legs, for example may indicate that the peritoneum is irritated

During a physical examination the patient s feelings should be respected One who is nervous will be made more so by rough handling One who is abnormally shy will not be completely relaxed when first undraped And most women resent being exposed unnecessarily They prefer to have covering sheets and do not like intruders during the examination Of course, a nurse should always be present at this time—if for no other reason than to provide protection for the physician—but she should be helpful rather than officious and domineering Furthermore, there are times when such help may be urgently needed unexpectedly

The need for a thorough physical examination before treatment is instituted is axiomatic but requires emphasis Too often physicians pay attention only to the patient s chief complaint But think what would happen, for example, if a physician were to give thyroid medication for some immediate objective such as weight reduction when exophthalmos and other signs of excessive thyroid activity were present but carelessly overlooked?

After the examination has been completed a diagnosis may or may not be possible without additional radiologic or laboratory procedures The situation should be explained to the patient in simple, understandable language This explanation is important to obtain the full cooperation of the patient and to prevent misunderstanding later, as the patient might otherwise appear surprised at the costs of such supplemental diagnostic procedures

Essentials of Treatment

ETHICAL AND LEGAL RESTRICTIONS

When the diagnosis has been established and a therapeutic regimen is to be initiated the physician should consider the moral and legal restrictions which may be involved Much of this is discussed elsewhere in the book Although he is expected to render aid to all patients who need help the physician should never forget his responsibilities before the law especially when there are suspicious circumstances connected with a patient s visit If a patient dies if poisoning or foul play is suspected if criminal abortion is surmised or if the patient has been involved in an accident special legal considerations are necessary

Other legal restrictions that must be considered when prescribing drugs are included in the Harrison Narcotic Act the Federal Food Drug and Cosmetic Act and certain state laws The Council on Pharmacy and Chemistry has reviewed the effects of the Harrison Act and the Federal Food Drug and Cosmetic Act on prescription writing in *The Journal of the American Medical Association* August 6 1949 page 1159 Whereas the Harrison Act has been familiar to members of the medical profession for many years the Federal Food Drug and Cosmetic Act is just coming to *the general attention of the medical profession* because of recent decisions and proposed amendments which affect some long standing prescribing and dispensing habits According to current interpretations a prescription cannot be refilled without authorization from a physician

Prescription and Over the-Counter Drugs

There is some confusion concerning the difference between a prescription and an over the counter drug The provisions of the Federal Food Drug and Cosmetic Act are so written that they permit over the counter sale of any drug whose labeling bears adequate directions for each and every use In addition evidence of the safety of the dosages which are recommended in the directions must be presented Drugs for which such general directions cannot be written are classified as prescription items and their labels must bear the legend, '*Caution, To be dispensed only by or on the prescription of a physician [or dentist or veterinarian]*" The Act thus legalizes the right of self medication by the public, but, unfortunately, the distinction between over the-counter and prescription drugs is not definite enough to prevent confusion concerning the status of many drugs

Recommended Practice"

The physician also bears a legal responsibility to utilize a drug in accordance with recommended practice The labeling usually contains sufficient information for the physician to employ the drug wisely as far as the route of administration and precautionary measures are concerned Occasionally accidents result from the administration of a potent drug because someone neglected to read the container label at the time the drug was administered A physician is generally advised not to use *an agent unless he is familiar with its action,* but even familiar drugs can be a source of danger since many potent remedies are available in a variety of doses and dosage forms which are not readily distinguished unless the label is examined carefully Various attempts have been made to warn the user at a glance of the product s nature but it is still necessary for the physician or whoever uses or prepares a drug to read a label carefully in order to be certain of the identity and quantity of what he is using It will probably never be possible to get sufficient

distinctive colors, emblems, or numbers to differentiate all dosages and doses Furthermore, this method is limited by its dependence upon memory There is no easy shortcut, nothing can replace constant vigilance and careful reading of labels The user, by acquiring the habit of checking the drug's label deliberately, rather than relying on its appearance or on the word of an associate, will avoid errors Drugs should be labeled properly, but warnings and directions for use must be read by the person administering the drug to make them effective If a solution or other dosage form looks questionable, it should be discarded If a label becomes detached and one cannot be certain of the nature of a drug, it should not be used

Although the fear of litigation and the possibility of heavy damages may make the physician more cautious, part of the remedy lies in impressing all medical students interns, and residents, while they are still in their training periods, with the dangers associated with the misuse of drugs This will encourage the development of habits in hospital personnel and private physicians which will keep possibilities of confusion to a minimum The misuse of a drug may mean loss of life for which the physician bears the moral and legal onus

With these responsibilities constantly in mind the physician should select the therapeutic regimen best suited to meet the needs of the patient It is better, as a rule to adhere to accepted methods of treatment if the ailment is following its normal course and is uncomplicated by previous therapy The patient usually requires specific instructions pertaining to bed rest, nursing care, hygienic privileges, exercise, and diet Whenever these are issued they should be stated in a way that the patient cannot misunderstand, otherwise, treatment may be only partially effective Written instructions are preferable to verbal and should be legible whether typewritten or written by hand The importance of this cannot be stressed too strongly

Experimental Therapy

ONE of the most perplexing problems confronting the physician is the place of new therapeutic measures in his practice Under certain circumstances, new approaches are forced on the physician, such as when accepted methods of treatment fail or when better known methods are either unavailable or would not alter the inevitable course of the disease However, this does not imply that selection of new means of treatment should be haphazard or based solely on the claims of pharmaceutic manufacturers and their detail men The selection should be deliberate and studied and based on sound clinical evidence The announcements in the daily press of advances in research obviously create problems for the physician The very fact that news agencies report these announcements and that reporters attend medical meetings reflects the absorbing public interest in matters of health As a result, the physician is often confronted by a patient who practically demands that the latest method of treatment outlined in the newspapers be employed in his case These demands should not be brusquely dismissed but should be discussed with sympathy The physician should ask for himself and his patient such questions as whether the advances are ready for practical application or are based on animal studies alone Were

the results obtained from enough cases to have statistical significance? Had the experiment been published in a reputable medical journal or was it merely announced in newspapers without detail sufficient for sound appraisal?

With such questions for which there are often inadequate answers the physician can indicate his unwillingness to make his patient an object of uncontrolled experimentation Nevertheless he must be constantly on the alert for the latest treatments so that he may save lives reduce suffering and shorten convalescence A decision is often difficult but the importance of its soundness cannot be stressed too strongly An error in judgment may mean someone s life

It is unnecessary except for emphasis to belabor any particular point involved in the misinterpretation of scientific data However it is impossible to emphasize too strongly the need for examining critically all new proposals and for discarding doubtful ones This is not a plea for obstructionism Rather it is a plea for moving forward with planned assurance—a plea for *progress without disheartening periods* of regression Control of health is often an intricate proposition Cure of the sick is even more vulnerable to disturbing influences Treatment of many chronic diseases such as tuberculosis and arthritis is accompanied with disappointments and setbacks which even though temporary, bring indecision doubt and disappointment These setbacks may frequently prolong suffering cause irreparable damage, and waste valuable time In the past, the lack of laws against false advertising allowed the salesmen s adjectives to raise false hopes Today there are laws which help reduce such tragedies but they can exert only a *limited effect on the over all* problem

For practical therapeutics, the claims of *advances in medical research can* be divided into several groups

1 Those that are worthless and are the result of willful deception or careless thinking
2 *Those that are strictly in the field of ex* perimental investigation and require further study before their value can be determined clearly and their general use advocated by competent authorities
3 Those that are of proved value when limited to certain uses
4 Those of more general usefulness but not of sufficient importance to warrant their replacing completely, other measure of treatment Usually these drugs or technics supplement established procedures or, at best serve as alternate measures when standard practices fail or are contraindicated
5 Those that are demonstrably superior to previously known agents or that provide effective treatment for the first time

It is possible, of course for confusion to arise as to the rightful category for a specific innovation in therapy The ways by which confusion may develop are varied as are the methods by which it may be perpetuated For example an author reporting a piece of research may misinterpret some of his findings or he may draw conclusions not justified by the data A writer in the popular press in order to interest his readers may depend more on fantasy than on fact and inject conclusions into his article which were never advanced by the researcher A reader of scientific or popular articles may resort to wishful thinking in his interpretation of the material As a result, he may himself expect (or lead his readers to expect) miracles

Present day insistence by scientific personnel on factual reporting and truthful interpretation of data *are encouraging* Encouraging too is the establishment of liaison between popular writers and scien

tists through public relations offices through recognition of agencies which secure advertisements and data and through other activities that are serving to minimize misunderstanding between the medical profession and the public

The Ultimate Purpose of Treatment

IN THESE days of seemingly endless drug miracles it is not difficult to become so engrossed in the specific actions of drugs that the ultimate purpose of medical treatment is overlooked This purpose is not the cure of some infectious disease in a particular patient but rather the control of disease and thus the procurement of better health for the public Too readily we think of the immediate effect rather than the ultimate end the quick recovery from an acute illness rather than the saving of life, restoration of normal health and continued economic security This security in turn, relieves the community of a financial burden which it or the state would otherwise have to bear if a family were bereft of a provider through death or chronic illness

QUACKERY

The physician must beware of those who practice willful deception when introducing a cure The patient and even the physician himself, may become a victim of wily schemers who hide their quackery behind seemingly legitimate organizations These promoters generally follow a characteristic pattern They adopt a high sounding name for some shadowy organization—a name which implies that the organization carries on research or is affiliated with a well known religious political or social group Then a spokesman for the organization announces a cure' for a chronic often hopeless disease Mysterious secret formulas or physical emanations are used for treatment with allegedly miraculous results Testimonials from reputedly cured cases are frequently a part of the promotion and the news of the 'cure spreads by word of mouth through the community and occasionally through the entire nation Inquiries by responsible authorities or by medical societies are met with stony silence or with a verbal blast which declares that the organization is being persecuted by organized medicine These attacks imply or assert directly, that physicians do not wish to allow miracle drugs to be placed on the market because the practitioner will lose the money which results from continued unsuccessful treatment of chronic diseases Such diatribes against organized medicine are ridiculous not only because they ignore the medical profession s ethical standards but also because they neglect the obvious fact that a physician s reputation and economic success are based upon cures and not on unsuccessful treatment The tremendous financial success of some of these panderers to the hopes of unfortunate chronically ill persons may lure some of the morally weak members of the profession to collaborate with them Patients with a chronic or incurable disease should be warned by their family physician of the existence of these quacks The practitioner himself should never be guilty of using a remedy whose formula is a secret or whose supposed ingredients cannot be found in chemistry or pharmacologic texts If in doubt he may direct an inquiry to the Council on Pharmacy and *Chemistry of the American Medical* Association which will furnish him with information on the legitimacy of the

treatment At every opportunity, the physician should make the public aware that ethical medicine does not countenance secret methods of cure, and that it insists upon proper systematic evaluation of drugs and wide dissemination of knowledge throughout the profession concerning their preparation and action

Evaluation of New Drugs

TWO organizations provide much help to the medical profession in screening new drugs One of these is the Food and Drug Administration which has as a part of its responsibilities the practical application of the Federal Food, Drug and Cosmetic Act The other is the Council on Pharmacy and Chemistry of the American Medical Association The provisions of the Food and Drug Act are concerned primarily with evidence of the safety of self administered drugs The Council on Pharmacy and Chemistry is concerned not only with safety but also with claims made for new drugs When in doubt, either agency may be consulted for information concerning preparations

Regardless of the glibness of the advertising or the alluring claims made for a drug the physician should remember that he alone bears responsibility for its use Therefore he should insist on knowing the standards by which a new drug has been evaluated His questions regarding the safeness and efficacy of a drug must be satisfied by a mass of evidence secured under controlled conditions through several phases of investigation The drug should have been studied in the laboratory and in the clinic The details of these studies depend upon the nature of a drug s ingredients and its intended uses However, all investigations should follow a general plan which will permit a thorough understanding of the usefulness and of the toxic properties of the drug

In the laboratory, the biochemical, pharmacodynamic, and chemotherapeutic effects of the drug should be thoroughly evaluated in experimental animals The toxic propensities of the agent for various organ systems should be adequately investigated under conditions approximating the intended use of the product in human beings In general, such studies embrace acute subacute, and chronic toxicity, local effects effects upon reproduction, upon nutritional state, and upon the influence of environment

The selection of animals for the investigation of new drugs is important because qualitative as well as quantitative differences exist between animal species in their reactions to drugs Some species are unsuited for demonstrating certain effects Methemoglobin for example, is not readily produced in rodents and, if the drug is suspected of causing this reaction, rats rabbits and guinea pigs are not suitable test animals Rabbits are not usually satisfactory for studies in blood pressure as they often react uncertainly

A critical review of experimental studies is necessary before using a drug on human beings and the following points should then be considered (*Journal of the American Medical Association*, December 9 1944, page 958)

1. Has the drug definite and desirable pharmacodynamic or chemotherapeutic actions?
2. Are its actions constant and reproducible?

Licensure

State licensure, of course, is a prerequisite to the practice of medicine A physician who happens to come face to face with an emergency while traveling in some state in which he is not licensed need not feel entirely impotent however He may render such first aid assistance as may be necessary and he may go further than that if *a bona fide emergency exists and it is impossible* (not just difficult) to get the injured person to a licensed practitioner Physicians who customarily vacation at the same place each year should not attempt to establish a secondary practice in that place on the emergency theory however, they *should meet the licensing requirements of* that state

BUSINESS AND PROFESSIONAL RECORDS

A physician's business and professional records should be one of his most valued possessions His business records, which are extremely important in this day and age, should reflect accurately his income and justify his claimed expenses One never knows when the revenue agent may pay a visit Likewise one never knows when the process server may appear with an order to produce certain records in court and therefore a physician's professional records also should receive meticulous attention They should indicate the diagnosis in each *case together with a notation* about the treatment rendered and the date thereof In fact it would be wise to include not only treatment rendered but treatment recommended as well

A physician may not force a patient to submit to a particular course of treatment or to go to a particular (or any) hospital When however a patient refuses to undergo a suggested treatment or fails to follow directions connected with the treatment *adopted or fails to appear* at an appointed time the physician should not be held responsible for the poor recover which a patient, under such circumstance might make He therefore, should not hesitate to call such dereliction to his patient attention and to retain in his records notation to that effect The record shoul also contain references to diagnostic aid used such as roentgenograms electrocardiograms etc Such aids are the property o *the physician or the hospital which make* them not of the patient The patient pay for the diagnostic opinion, not the film o the chart

Prescriptions

Prescriptions on the other hand, are no *the property of the physician who write* them or of the patient, but rather of the pharmacist who fills them In many instances pharmacists are required by law t retain prescriptions (for narcotics for example) for a certain period of time after they are filled Even apart from this however custom and usage has developed in most areas to the point where prescriptions are naturally retained by the pharmacist although there is nothing to prevent a *pharmacist from agreeing to give the pur*chaser a copy of the prescription Whether or not a prescription may be refilled depends on the physician and the law of the particular state and the law of the United States Prescriptions for some drugs, such as narcotics and barbiturates and others which may be sold only on prescription may not be refilled unless the prescription specifically authorizes it together with the number of times which it may be refilled *Where the refilling of a prescription is not* specifically regulated by law the physician must use his own discretion He should consider the criticism often made that physicians refuse to permit the refilling of prescriptions just so they can force the patient into making another office call This might be an unnecessary increase in the patient's cost of adequate medical care

Patient Consent

The physician s records should also contain copies of all consents received from patients Whenever any operation, examination, treatment, or procedure which might technically constitute an assault and battery is contemplated, the physician should be protected by the written consent of the patient when that is at all possible Oral consents are perfectly valid but are harder to preserve and prove should the necessity for doing so arise No consent is necessary for the performance of procedures required by law, such as compulsory vaccination compulsory sterilization, and the like, or procedures arising by virtue of an emergency and which are necessary to save a person s life In all other cases consent should be obtained from the patient (if an adult and of sound mind), from the patient s parents or guardian (if a minor or noncompetent) or from the patient s spouse (if the operation is likely to result in sterility) Consent should also be obtained for the performance of an autopsy, either from the surviving spouse, parents, children, etc or the person having custody of the body All such consents should be as specific as possible—blanket consent forms are undesirable—and the consent obtained should be strictly followed It should be remembered that a consent is no defense to an unlawful act

In addition to getting and preserving an adequate consent, a further cautionary procedure, when making gynecologic or similar examinations, is to have a nurse or the patient s husband present or within easy hearing at all times Occasionally a mentally disturbed patient will charge that a physician mistreated her during an examination The presence of a nurse or of the patient s husband will afford protection to the physician from unwarranted charges of this nature

Coupled with the patient s consent is the physician's agreement to perform the services contemplated therein It is perfectly all right for a physician to contract for the performance of a particular operation or course of service (such as care during confinement), but it is unwise to promise the accomplishment of specific results The recuperative or restorative powers of each individual differ and a person may fail to recover even though the highest standard of care was applied to the case If the physician has promised certain results, however, he is liable for damages for a breach of contract if those results are not obtained and in such cases he may not fall back upon the fact that he was in no way negligent

Reports to Authorities

The laws of the several states differ in their requirements for the reporting by physicians of certain diseases, gunshot wounds etc The physician should make it a point to know and to abide by the laws of his own jurisdiction The local health officer and police department can usually furnish the necessary information in this regard

Privileged Communications

The relationship of trust and confidence existing between physician and patient, which gives rise to the privileged communication laws found in some states, should not be used as a cloak to hide a crime The physician has the same responsibility as any other member of the public so far as assisting law enforcement officers is concerned It is true that one of the honored practices of the medical profession is to keep confidential information relating to patients This confidence is not broken by observing the reporting of laws referred to above or by appearing in court in response to a lawfully issued subpoena, and producing records and answering questions A physician is not required to stand in contempt of court to protect his patient's confidence.

As long as the science and art of medicine continue to change and advance, there will always be some practices and procedures that have not yet been tested in court as to their possible legal implications, such as artificial insemination or sterilization of an unmarried woman without therapeutic need Extra care should be observed in obtaining an adequate consent in all such cases Even then, as indicated above such consent might prove to be useless if the procedure were subsequently held to be unlawful

In conclusion, it should be remembered that prevention is the best defense against a suit for malpractice The following brief sentences will indicate a few general techniques for preventing some, if not all, legal entanglements

Abandonment Never abandon or neglect a patient without good reason, and then only after timely notice has been given and a qualified substitute rendered

Assistants Give nurses, interns and other assistants detailed instruction as to method and course of treatment

Cleanliness Make cleanliness a routine technique in hospital, office and home

Consent Obtain proper consent (preferably written) before you begin any surgical operation, treatment or autopsy

Consultants Do not hesitate to call in specialists for consultation if you think that a specialist's knowledge and services are necessary

Diagnosis A patient's complaints are often valuable diagnostic aids and should not be overlooked or ignored

Equipment Equipment in hospital and office must be maintained in perfect condition at all times

Examination Make the most thorough and complete examination possible under the circumstances Utilize available laboratory facilities

Fads and Hobbies Do not use or recommend any fad or unproven method of treatment nor 'ride a hobby'

Guarantee Never promise or guarantee a cure as a result of any special operation medication or course of treatment

Instruments Use only sterile instruments in any operation

Labeling Be sure that all preparations are adequately labelled and preserved

Loose Talk Make no adverse criticism of care or treatment a patient has received from another person

Medical Progress Keep abreast of new treatments and techniques, read approved medical publications, take refresher courses, attend scientific meetings, etc

Morals An office assistant or a nurse should be present or within hearing distance while examining a nude or semi nude patient Prohibit presence of laymen

Records Make sufficient clinical records of diagnosis and course of treatment both in hospital and office

Sponge Count Keep an accurate count of sponges, clamps, retractors etc, used in any operation in a body cavity

2. Pharmacologic Principles in Treatment

CHAUNCEY D. LEAKE

IT IS now widely recognized that knowledge of the general principles of pharmacology is helpful in the practical clinical use of drugs Such knowledge is of immeasurable aid when the physician must choose the most effective chemical for a particular clinical situation

It is also particularly helpful to understand what factors determine the intensity of drug action to know something of the general principles of dose-effect and time concentration relationships and to appreciate how drugs act An intelligent grasp of the general principles of current pharmacology and of the basic concepts involved will permit more intelligent more effective and more economical use of drugs with greater satisfaction both for patient and physician

Development of Pharmacology

PHARMACOLOGY as the study of the biologic action of chemicals has now been subjected to a century of intensive investigation During this time in spite of handicaps it has made significant contributions to our scientific knowledge Many of its possibilities however have been neglected because of its inherited dependence on medicine and because of its subservience to therapeutics It was impossible for pharmacology to become a science until substances of constant physicochemical properties became available The science of chemistry was necessary for the development of the science of pharmacology Crude materials varied too greatly in composition and in biologic effects to permit anything better than deductions of a rough qualitative nature with respect to their pharmacologic properties Yet for centuries such lore had accumulated and had been applied to therapeutic problems with variable success

Pharmacology and Medicine

Pharmacology is the study of the action of chemicals on living organisms This action may be beneficial or harmful and

the organisms may be plants or animals Pharmacology is thus a broad scientific discipline, but its findings are applied chiefly in medicine However, other applications are rapidly developing in agriculture industrial hygiene, law, and even in sociology Pharmacology is closely related to other scientific disciplines such as biochemistry, biophysics, physiology, microbiology, pathology and pharmaceutical chemistry

It is necessary to differentiate between the *action of drugs* on living things and the *practical use* of drugs in medicine or in other fields of application The process of acquiring knowledge of the action of chemicals on living things is a scientific matter The application of this knowledge to the benefit of a sick patient calls for the exercise of judgment and discrimination

Pharmacologists are responsible for acquiring knowledge about the actions of chemicals on living things Physicians are responsible for the wise and judicious application of the available knowledge for the benefit of the patient To succeed, physicians must possess and appreciate the fruits of the work of pharmacologists and must understand the basic principles of their application

Folklore Pharmacology began with observations of the action of crude plant animal and mineral materials when tried for food or after coming in contact with the skin Primitive peoples developed elaborate folklore regarding the applications of such observations to the treatment of disease Many of these ideas were surprisingly sensible For example, the Modoc Indians of northern California observed that the eating of the bark of a certain tree produces purgation They then sensibly used this bark when constipated In this way cascara sagrada was introduced into medicine

The ancient Egyptians collected their slowly acquired drug lore into recipe books which recommended the use of various preparations in different clinical conditions

Complex prescriptions containing many different ingredients probably were developed during the compilation and transcription of early manuscripts when the compiler found several materials recommended for the same purpose with no indication of relative effectiveness This kind of "shotgun therapy remains a constant temptation even today

Development of Systems Dioscorides, in the first century A D, originated a different system, which was based on a medical application of the botanical works of Theophrastus, the pupil of Aristotle This system led its followers to describe as carefully as possible the individual crude materials of plant, animal, and mineral origin used in medicine, and then to indicate how each was to be prepared and administered, and for what purposes each was to be used This method of organization on the basis of the materials used, rather than on diseases to be treated, was subsequently followed in the development of modern pharmacopoeias The great Roman physician, Galen (A D 130–201), in his extensive compilations, used the therapeutic procedure of recommending various drugs and combinations for various disease conditions These two separate and distinct methods of organizing knowledge regarding drugs have been followed to the present day

MODERN PHARMACOLOGY

Modern pharmacology began in the eighteenth century with the establishment of chemistry on a quantitative basis as a result of the contributions of Lavoisier (1743 1794) Crude drug mixtures were analyzed for their active principles, which then could be studied systematically Since many of the active chemical agents found in naturally occurring crude drugs were not ideal for use in medicine chemists be

gan to search for better or more purified agents. The effort was directed chiefly towards increasing the desired effect and reducing the toxicity. As a result, many thousands of related synthetic compounds have been brought to pharmacologic trial.

Evaluation of Drugs

THE most important criteria for the choice of a drug for a particular medical purpose are low toxicity, desired activity, prompt and easily controlled effect, absence of untoward reactions even after frequently repeated administration, ease of administration and manufacture and low cost. It is essential that practicing physicians give attention to these criteria for the choice of drugs for use in their patients.

DRUG STANDARDIZATION

To be certain of reasonable uniformity of clinical response to the same dose of a drug, it is necessary for the drug to be standardized. This was recognized as long ago as the sixteenth century when Valerius Cordus (1515-1544) prepared a formulary for the use of the druggists of Nuremberg. This formulary was adopted by the senate of the city as the standard to be followed

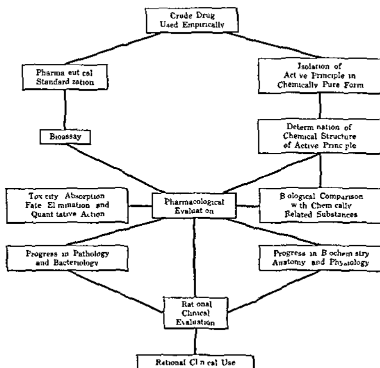


FIG 1 The logical and historical position of pharmacology in the rational use of chemical agents in medicine (Modified from C D Leake The pharmacologic evaluation of new drugs *J.A.M.A* 93 1632-1634 1929)

by all druggists It became, then, the first official pharmacopoeia The local physicians were now assured that the drugs they ordered by the standard name always would be the same They could thus expect reasonable uniformity of effect from the same dosage of a standard preparation

The drug standards adopted in pharmacopoeias are usually given legal support For example, the *U S Pharmacopoeia* was originated in 1820 at a national convention of physicians, druggists, and public officials that was organized by Lyman Spalding (1775 1821) It has been revised decennially to 1942, when a plan for revision every five years was adopted This book and its supplements and the National Formulary are official compendia in the United States and are recognized in the Federal Food, Drug and Cosmetic Act Similarly the *British Pharmacopoeia* is official in Great Britain and elsewhere, for example, Canada

Isolation of Active Principles

A great advance in standardization was possible when the active principles of crude drugs were isolated in chemically pure form This was first accomplished by F W Sertuener (1783 1841) in the early part of the nineteenth century when he obtained crystalline morphine from the crude mixture called opium The crystalline substance could now be made to conform to specific chemical standards A more precise relationship between dosage and effect thus became possible This process of isolating and identifying of the biologically active chemicals in crude drug mixtures has proceeded for a great variety of alkaloids, steroids, and other types of compounds from plant and animal sources, including hormones, vitamins, antibiotics, and enzyme mixtures

Enforcement of Standards

The full value of establishing drug standards depends on the establishment of three areas of agreement which all physicians should be prepared to support (1) agreement on what constitutes the standard of reference, (2) agreement on the definition of the drug and on adequate methods of estimating its purity, and (3) agreement on enforcement of the standards Although difficult, agreements regarding drug standards have even been achieved on an international level The successful, intelligent use of drugs is impossible without an appreciation of the importance of drug standardization

Nomenclature

The use of public or generic names of drugs is a particularly practical matter for the physician It means much saving in money, especially in bulk purchases which is of major concern to hospitals It also means savings to private patients, for the pharmacist need not stock multiple brands of the same chemical and therefore may reduce his overhead costs and purchase more economically

A chemical agent sold under a "trade name" at times may cost much more than the same drug sold under its public or non protected name It is important for physicians to become acquainted with the generic names, if available, of drugs even if patent rights may have existed, and always to use such drugs under their public names When physicians do a lot of dispensing it is economical to use drug names as listed in the *Pharmacopoeia* or *New and Nonofficial Remedies* and when using combinations of drugs to follow the well tested formulas in the *National Formulary*

Appraisal of New Drugs

SYSTEMATIC appraisal of the value of new drugs developed for medical use should begin with an exhaustive study of toxicity on single and repeated dose in several species of animal All phases of possible toxic action should be analyzed and described for the benefit of the physician who should then be offered full information on rates and ways of absorption in the body What happens to the drug in the body should be studied and described Physicians should be informed regarding the rates of detoxification and the rates and modes of excretion of drugs General and special pharmacologic properties of drugs should be described in detail This information should be offered in comparison with related and commonly used chemicals offered for the same purpose The physician is then in a position to make a rational judgment for himself as to the best drug for the particular purpose he has in mind

The physician should insist on receiving this type of evidence from commercial pharmaceutic concerns The physician's judgment should tell him for what purposes to use a drug It is not the function

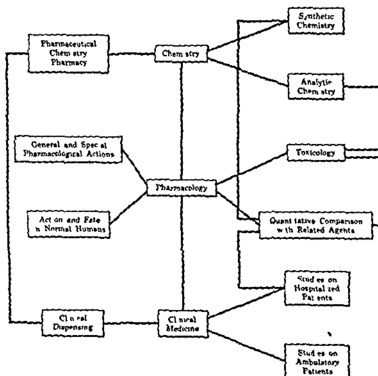


FIG 2 [illegible]
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of commercial pharmaceutic concerns to tell a physician how to practice medicine It is their responsibility, however, to give the physician full scientific information regarding the drug they are promoting

Factors Modifying Drug Action

THE chief factors modifying drug action are dosage, ratio of the rate of absorption of the drug through the body to the rate of its destruction or excretion, physicochemical properties of the drug and individual peculiarities of the patient to whom the drug is given The relation of these factors to the intensity of drug action may be indicated by the shorthand formula

$$I = (f)\, D\, \frac{rA}{rE} \times P \times S$$

where I is the intensity of drug action D is dosage rA is rate of absorption or distribution of the chemical through the living tissue involved rE is the rate of excretion or removal of the drug from the living tissue concerned P represents the physicochemical properties of the drug and S the peculiar individual characteristics and sensitivities of the particular patient or living tissue concerned

DOSAGE

By dosage is meant mass of chemical per mass of body tissue excluding fat This suggests the importance of dosage on the basis of milligrams of drug per kilogram of body weight Many of the newer drugs are being introduced for use in this manner Drugs with a more general and less toxic action may be given by average dose but for precise drug use *it is wise* to determine dosage in milligrams per kilogram of body weight or as millimol equivalents

Sometimes when new potent drugs are being developed dosage is expressed in units of biologic activity This can result in much confusion Units of biologic activity are helpful in scientific study and are necessary clinically when there is no agreement on a standard preparation However when agreement has been reached on a standard it is merely necessary to express dosage in terms of ordinary weight and volume measurement of the preparation as adjusted to the requirement of the standard Thus the aromatic fluid extract of cascara sagrada is administered in ordinary dosage by volume since it is a standardized preparation It could nevertheless be administered in terms of purgative units However this would be foolish *On the other hand unit dosage of insulin* is still followed clinically Unit dosage of such a potent drug as vitamin D may be dangerously confusing since the large number of units recommended for administration may give a false sense of relatively low toxicity Actually vitamin D is a very potent and toxic drug A milligram of the purified compound contains 10 000 units

MODE OF ADMINISTRATION

The mode of administration profoundly modifies dose effects because it influences the rate of absorption of the drug It is particularly helpful for the physician to study technics of medication *to obtain the* most satisfactory results in patients For example absorption of gaseous agents across the respiratory mucous membrane is very rapid Intramuscular injection offers steady absorption for drugs in oil suspension Subcutaneous injection is not a par

ticularly satisfactory method of administering drugs, but it is widely used The most rapid distribution is obtained when a drug is given by vein Sometimes a drug may be injected into the spinal canal It is wise to remember that drugs may be absorbed from the mucous membranes of the vaginal tract, the ear, or the eye Sometimes a drug given only for local effect at the point of application may be absorbed and produce a systemic reaction

RATE OF EXCRETION

It is also helpful to know something about the rate of drug destruction or excretion This gives a clue to the important problem of how frequently to repeat administration Many drugs such as penicillin or the sulfonamide compounds, are rapidly excreted in the urine and require frequent administration to maintain the concentration necessary for effectiveness

Sometimes it is possible to combine rapidly excreted drugs with other substances to delay excretion This has been done successfully with penicillin, insulin and pituitary preparations

Many drugs such as aspirin amidopyrine, sulfonamides local anesthetics and aniline are detoxified by combining with amino acids in the body All drugs whose molecules include a ring structure with amino groups or phenolic hydroxyl groups also may combine with amino acids When this occurs allergic responses may appear in sensitized tissue A physician cannot tell which patient may show the allergic reaction or where it may occur but he should expect such reactions in at least 5 per cent of patients

PHYSIOCHEMICAL PROPERTIES

The physiochemical properties of drugs are important because of their action in the body If the drug is more soluble in oily material than in water, it will tend to concentrate in the oily parts of the body Most drugs acting on the nervous system where tissues of greatest functional importance are found have a high oil water solubility ratio The capacity of drugs for oxidation or reduction as well as their polarity properties are important in respect to their reaction with enzyme systems in cells These problems will become increasingly significant as more is learned of the implications of these properties and physicians should be prepared to acquire this new knowledge as it develops

THE INDIVIDUAL PATIENT

Highly pertinent from the physician's standpoint is the estimation of the peculiarities of his individual patient with respect to drug reaction Age sex metabolic state, constitutional factors and allergic tendencies must be appraised Careful clinical judgment is required to evaluate these individual factors in a particular patient as each may influence drug action

The *metabolic rate* is high during infancy but diminishes quickly to rise again gradually until adolescence It then maintains a plateau until the fourth or fifth decade when gradual decline begins The estimation of metabolic status is a difficult clinical problem but it is significant in connection with the activity of many different types of drugs

Some drugs such as morphine, do not follow ordinary rules regarding the effects of *age* Infants and old persons in general are more sensitive to morphine than persons in the prime of life

It is particularly important to appraise the autonomic nervous balance Some persons may be peculiarly sensitive to sympathetic drugs whereas others may show a higher sensitivity to drugs acting on the parasympathetic system It is most important to appraise if possible the allergic tendencies in a patient

DOSE-EFFECT RELATIONSHIPS

Different persons will respond differently to the same dose of the same drug This can roughly be represented by "distribution curves' in which increasing intensity

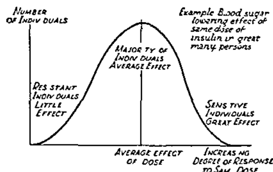


Fig 3 Typical distribution curve of individual reactions to a drug

of reaction to the same dose is indicated along the horizontal axis, while the vertical axis shows the number of persons grouped with regard to the same intensity of reaction In general there will be some persons who will show a relatively small response

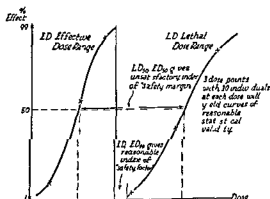


Fig 4 Graphic explanation of safety factor in a drug

The great majority will show the 'average effect' A small number of persons may show a particularly intense reaction from a dose that might produce no effect in *the less sensitive person*

When results are accumulated with reference to all or no effect (as cure or death), the curve is sigmoid and shows the percentage of persons reacting, when arranged on the vertical axis, to increasing dosage on the horizontal axis Such curves are particularly important in the quantitative estimation of toxicity and effectiveness

*Safety Index Because of its ease of es*timation under experimental conditions, the 50 per cent point on the curve is usually taken as the standard of reference Thus, *ED_{50} refers to the 50 per cent effec*tive dose, that is the dosage which will be effective, in the intensity desired, on 50 per cent of the organisms to which the drug is administered In the same way, *LD_{50}* refers to the dosage at which 50 per cent of the organisms to which the drug is administered may be expected to die The ratio between the *ED_{50} and the LD_{50}* of a drug under standardized experimental conditions is sometimes referred to as the "safety index

In clinical practice, the physician is not interested in the dosage which will produce the desired effect in only 50 per cent of his patients, nor is he interested in the dosage which may kill 50 per cent of his patients *He must be aware however, that the effec*tive dose range of a drug may overlap the lethal range or the range of toxic reaction This happens for example, with such *drugs as emetine hydrochloride.* Since the mechanisms of desired action and of death may be different, the slopes of the curves may differ and overlap may readily occur It is important, then, for physicians to require pharmaceutic manufacturing houses to give precise information on the *ED_{99}* with relation to the *LD_1*, that is the ratio between the dosage which might be expected to produce the desired effect in practically all patients and the dosage that might produce an untoward reaction only in the most sensitive 1 per cent of his patients

TIME-CONCENTRATION RELATIONSHIPS

Time is an unavoidable factor in the biologic response to drugs For certain drugs, such as the inhalation anesthetics the effective concentration for anesthesia if maintained long enough, might produce untoward or even lethal effects Accordingly, it is necessary to have data expressed in time concentration curves This may assist materially in estimating absorption and excretion gradients in relation to time and concentration for many important types of drugs One wishes, of course, to obtain a concentration which will produce the desired effect within a reasonable time, but which will not produce undesired effects even if maintained for a relatively long period

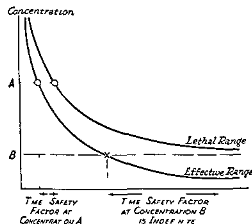


Fig 5 Time-concentration curve

The concentration of a chemical in any particular living tissue at any given moment after administration is calculated from the product of dosage (mass of chemical per mass of living material) and the ratio of the rate of absorption into the tissue to the rate of its removal from it There is a direct relation between concentration and intensity of effect

Mechanisms of Drug Action

WHILE the dose-effect relationship of drugs long ago was regarded as a scientific problem for pharmacology, the question of the mechanism by which drugs act was not raised scientifically until the nineteenth century

With the development of modern chemistry, and the isolation and identification of the active principles of crude drugs in crystalline pure form, it was possible for the first time to begin a quantitative study of drug action with particular reference to mechanism

François Magendie (1783 1855), James Blake (1815 1893) Oswald Schmiedeberg (1838 1921), and Claude Bernard (1813 1878) were leaders in developing scientific explanations of drug actions which culminated in the work of A C Brown (1838-1922) and T R Fraser (1841 1919), on the curare like effect of quaternary ammonium derivatives of various alkaloids, which led them to emphasize an extreme physicochemical position in the mechanism of drug action They postulated that the action of a drug is entirely a function of the chemical structure and energy relations of its molecule This approach has been brilliantly developed with the introduction of many new useful drugs by a host of chemists

Stabilization of drug standards and of criteria for quantitative study of drug action has resulted from the fundamental work of Trevan Gaddum Clark, and Burn The English symposiums and reviews on current pharmacology are most satisfying and deserve extended study

Molecular Theories of Drug Action

Recent studies on the mechanism of drug action have been directed toward the basic units concerned which are molecules of drugs in relation to living cells This has been well explored by A J Clark (1885 1941) and his English followers Clark called particular attention to the relatively small size of the molecules of a drug in comparison to the relatively large size of the cells on which they act He pointed out that the large number of molecules of a drug even in a small mass would compensate for the difference in size However, in many instances, as with cholinergic or adrenergic compounds, the number of *molecules capable of producing an effect* can be explained only on the basis of chemical reaction with a small active patch on the surface of the cell

Most of the current theories regarding the mechanism of drug action involve *surface phenomena* These concern surface tensions, polarity, template effects, blocking effects active patches and a competitive effect involving essential metabolites in complicated enzyme systems

Surface Organization of Cells To understand current theories of the mechanism of drug action it is essential to know something about the surface organization of cells According to the admirable summary by Davson and Danielli the cell surface is *composed of a double layer of oriented* lipid molecules with single flattened molecules of protein spread on the outside and inside These protein molecules may have reactive chemical groupings *exposed to the* surface to which various compounds in the intercellular fluid, including drugs may become attached On the other hand, certain ions may pass between the protein molecules into the lipid layer and eventually into the cell Other compounds in the intercellular fluid may disrupt the proteins on the surface *dissolve the fats in the* lipid layer, and thus profoundly alter the surface tension with resulting injury or rupture of the cell Certain molecules attaching to the surface of the cell may block *other essential molecules* from reacting with the cell in ordinary metabolism thus altering the activity of the cell

It is now known that many chemicals such as the sulfonamide drugs, act by interfering with essential *metabolites, particularly* vitamins, through competition due to their similarity of chemical structure It is also now well established that many drugs, such as organometallic chemotherapeutic agents, act by disturbing enzyme systems either *on the surface of cells or inside* them

Molecular Cohesion Frey Wyssling *has* indicated the chief means by which molecules adhere to each other in establishing the structural organization of cells and in reacting to give energy transference The four important processes are (1) *homopolar binding cohesion* by means of fitting of terminal hydrocarbon groups or between the long carbon chains of two hydrocarbon molecules between which the angles and distances between carbon atoms tend to form a template, and in which temperature plays a significant part, (2) *heteropolar cohesion* between terminal OH ions in which H_2O splits off, and where the state of hydration is significant (3) *heteropolar valence bonding* related to heteropolar cohesion, with particular reference to reactions between electronegative and electropositive ions, such as chloride and sulfate on the one hand and potassium magnesium, calcium, and sodium on the other, or where there is salt formation ester formation or amide condensation, and where *pH is highly important, and* (4) *homopolar valence bonding*, under the influence of variations in redox potential, as between S S and S H or in ether formation

The chemical character of a drug will determine into which of these protoplasmic

processes it may fit, and thus how it may alter cellular function

Hydrogen bonding is also important in drug protoplasm reactions as indicated by protein denaturation when hydrogen bonds are ruptured Many chemical compounds are dependent on H bond effects for their biologic action

Various kinds of drugs entering into this milieu may react with various components of the complicated enzyme systems or may compete with those molecules necessary for the normal metabolism of the system and thus interfere with its functioning Particularly important are the factors associated with protein synthesis and the energy yielding enzyme systems involving phosphorus, iron and compounds having high electron density under certain conditions

In spite of the complexities of drug action, certain relatively simple matters of general significance can be appreciated An important point always to remember is that drugs can only make cells do something they are already capable of doing No drug for example can make a muscle cell secrete urine No drug can restore a functional activity of a cell so damaged as to be incapable of that function

Biochemorphology Relation Between Chemical Constitution and Biologic Action

Physicians also should understand something about the relation between chemical constitution and biologic action of drugs This fascinating subject was first investigated by that remarkable physician James Blake (1815 1893) He classified the elements into groups on the basis of the biologic action of their salts These groups of course, correspond to what we now call the 'periodic table

It is interesting for instance, to find a similarity of depressant action among the various members of the aliphatic organic compounds Similarly, a pharmacologic property common to most alkaloids is rapidity of absorption and distribution and rapidity of destruction or excretion On the other hand, all steroids, including vitamin D sex hormones digitalis, and carcinogenic agents, are slow in action, with slow absorption and destruction, but the action lasts for a long time even from small dosage

As we learn more about energy distribution and potentiality we will be able more satisfactorily to predict possible biologic action of new chemical compounds Indeed some advance in this respect has already been made

An adequate discussion of the clinical application of pharmacologic principles would require a book rather than a chapter However, a brief consideration has been developed here even though the shortcomings of brevity are realized, to emphasize the need for understanding pharmacologic principles before drug therapy is instituted for any patient There are many sources of reference and several outstanding organizations from which therapeutic help and guidance can be obtained when needed It has little value however, if not properly employed, and proper employment is virtually impossible without an appreciation of pharmacotherapeutics Such an appreciation may mean the difference between partial and complete success in treatment even between life and death for the patient

3. Principles of Clinical Immunology

LOUIS WEINSTEIN

IMMUNOLOGY is defined by Boyd as the study of the procedures we use and of the mechanisms by which resistance is increased The field of diagnosis by means of immunological methods is called *serology* The means by which the host resists parasitic invasion is implied in the term *immunity* and includes both naturally occurring and artificially induced resistance The purpose of this chapter is to discuss the immunologic mechanisms of significance in the prevention and treatment of human infection diagnostic serologic tests are considered in Chapter 49 on diagnostic technics

Types of Immunity

IMMUNITY may be classified as follows

I *Innate immunity* (constitutional or racial)
II *Acquired active immunity*
  A Natural
  B Artificial
III *Acquired passive immunity*
  A Natural (congenital)
  B Artificial

The degree of effective resistance to infection is a function of the interaction between the defense mechanisms of the host and the invasive capacity of the parasite Immunity therefore must always be considered in terms of the invader and the invaded The degree of parasitism the number of the invaders and their localization or dissemination are the factors of importance Both specific and nonspecific mechanisms naturally present or artificially created are significant in resisting invasion or limiting spread of living agents or their products by the host it is only with these phenomena that this chapter is concerned

Total lack of immunity or complete resistance to infection are both very rare Clinical immunity falls between these two extremes The varying grades of resistance have been classified by Topley and Wilson and modified by Boyd for bacterial infections as follows

1 *Completely susceptible* (All or almost all infected individuals will develop fatal bacteremia Local lesions infrequent and minimal)
2 *Low grade immunity* (Fatal bacteremia less common Local lesions more frequent and more pronounced A small but increasing number of latent infections)
3 *Medium immunity* (Bacteremia and death much less frequent Local lesions common and relatively extensive Latent infections more frequent)
4 *High grade immunity* (No deaths, bacteremia infrequent and slight and transient when present Local lesions less frequent and extensive Latent infections most frequent or on decline)
5 *Complete immunity* if it exists (The animal is completely resistant to all attacks of the infectious agent)

ANTIGEN AND ANTIBODY

The terms antigen and antibody have wide use in any discussion of immunity They are usually defined in terms of each other An antigen is a substance which when introduced by artificial or natural means leads to the production of a material (antibody) which combines with or inactivates the antigen specifically An antibody is a soluble component of the serum or tissue fluids which develops after contact (by natural infection or artificial immunization) with an antigen Bacterial suspensions altered bacterial toxins living partially inactivated or dead viruses suspensions of rickettsiae, snake venoms, pollens etc, may all act as antigens Antibodies include agglutinins, precipitins, bacteriotropins, opsonins, virus neutralizing materials, bactericidal substances, blocking antibodies antitoxins, and antivenins

The mere presence of an antibody does not necessarily indicate resistance to infection Such antibodies as agglutinins and precipitins, while of the greatest significance in serologic diagnosis, are of little or no import in protecting against invasion by infectious agents The effectiveness of an antibody is dependent not only on its character and specificity, but also on its quantity, mere presence of virus neutralizing activity in a serum, for example, has no clinical significance unless its concentration is sufficiently large to inactivate the dose of virus with which a patient may come in contact

To discuss immunity in terms of antigens and antibodies alone would be to eliminate from consideration some of the most important mechanisms of defense Although acquired infection or active immunization often leads to the development of antibodies and specific active immunity, such resistance may exist without prior contact with antigen and be totally unrelated to the presence of demonstrable antibody of any type Thus, as pointed out in the classification of immunity, immune states result from either constitutional factors not dependent on prior contact with an infective agent, or from exposure during infection, or from active or passive immunization

The purpose of this chapter is to discuss some of the general principles of immunology as they have clinical application and to cite examples which emphasize specific concepts

HARMFUL IMMUNE RESPONSES

Although effective immune mechanisms are usually considered of benefit to the host, it is important to point out that some 'immune' responses may be harmful Some may produce disease and occasionally even death, such as serum sickness, the pollen allergies, Rh and anti Rh reactions, dermatitis venenata, anaphylaxis drug sensitization, the postinfectious encephalitides, and possibly acute diffuse glomerulonephritis, rheumatic fever, polyarteritis nodosa, dermatomyositis, and others included usually in the group of so called 'collagen diseases' Such deleterious immune reactions are not discussed in this chapter but are considered individually elsewhere in this text

I. Innate Immunity

THE term innate immunity applies to the methods of defense against infection available to the host which do not involve demonstrable immune mechanisms They are, for the most part, nonspecific and are concerned in the general protection against all types of infectious disease, in a few instances, however, they may exhibit a moderate degree of specificity Of all of the factors concerned in resistance those which make up innate immunity are of the greatest importance in everyday existence While certain humoral antibodies are operative and of greatest importance in specific diseases, they are probably relatively unimportant in guarding the host against invasion by the large variety and astronomic number of micro organisms with which he comes in contact in his daily life Against this constant barrage of parasites, mechanical defense mechanisms—heredity, race, nutritional status, tissue immunity, etc—are of the greatest protective significance

MECHANICAL FACTORS

Skin

The unbroken skin is one of the most important barriers against parasitic invasion It is not, however, completely invulnerable Over the exposed surfaces of the body such as the hands and face there are frequently minor abrasions and cuts as the result of the trauma of weather, shaving work, etc, and these minute openings may serve as portals of entry for micro organisms Some bacteria, *Brucella* for instance, are said to penetrate the unbroken epidermis The hookworms are known to invade the integument of the feet

There is some evidence to indicate that skin may exert a bacteriostatic and bactericidal effect on organisms which are present on it Thus, cultures of *Proteus vulgaris Escherichia coli*, or *Streptococcus pyogenes* painted on the normal epidermis are killed fairly rapidly There appears to be some fluctuation in this self sterilization, for example, it decreases in activity just before and during menstruation

Other Mechanical Factors

Mechanical factors are also of importance in preventing infection of the respiratory and gastrointestinal tracts The vibrissae in the nasal vestibule are probably the first line of defense against bacterial invasion since they are so situated anatomically that they may catch and retain any particulate material in the inspired air The mucous secretion of the respiratory tract, because of its viscid character also traps bacteria The cilia of the bronchial epithelium move organisms towards the upper portions of the respiratory tract There is some evidence that the mucous membranes of the respiratory tract may exert a bactericidal effect

In the gastrointestinal tract, in addition to the effect of gastric juice which will be discussed later, the speed of the movement of the contents prevents rapid and extensive multiplication of microorganisms The mucous membrane, particularly of the duodenum, exerts a lethal effect—mainly on nonpathogenic bacteria In the experimental animal in which portal bacteremia has been shown to occur, the liver is probably of the greatest importance in preventing generalized infection because it acts as a mechanical filter

In subacute bacterial endocarditis mechanical factors are probably the most important determinants As a rule, chronic endocardial infection follows bacteremia only if there is a site on the heart valve

mechanically suited for the implantation of the organisms, that is a structurally damaged valve In about 25 per cent of cases of subacute bacterial endocarditis the interruption of a mechanical factor which protects against invasion of the blood is of great importance The transient bacteremia, usually due to *Streptococcus viridans* that occurs in from 20 to 50 per cent of individuals after dental extraction is due to trauma to the gingival tissues with opening up of numerous blood vessels and forcing of bacteria into them by the pressure and suction incident to pulling of the tooth This invasion of the blood stream plus the damaged heart valve are the two most important factors in the pathogenesis of subacute bacterial endocarditis

CELLULAR FACTORS

The significant aspects of cellular immunity are related in the main to activity of the polymorphonuclear leukocytes and monocytes in the circulating blood and to the wandering and tissue histiocytes or macrophages

While phagocytosis in the *blood* occurs with greater rapidity and intensity in the presence of homologous sensitizing antibody opsonin this humoral factor is not absolutely essential in the process *Tissue* phagocytosis takes place at sites of invasion by organisms in the very early stages of an infectious process cells from both the blood and tissue participating in confining the bacteria to the area at the site of entry

Phagocytosis is of special importance in *protection against or in recovery from infection* due to gram positive cocci In pneumococcal pneumonia and streptococcal pharyngitis resolution and cure of the disease is effected for the most part, by phagocytic mechanisms before there is any effective quantity of humoral protective antibodies

The cells of many organs and tissues probably possess inherent antibacterial activity in the absence of any demonstrable humoral factors The bactericidal effect of the skin and the mucous membranes of the respiratory and intestinal tracts has already been discussed In some situations in which infection has already taken place, early resistance to invasion is related to cellular changes

HUMORAL FACTORS

The innate humoral factors of importance in resistance to infection may be divided into two categories (1) those which are true antibodies and (2) those which endow the tissue fluids with the ability to suppress bacterial or viral multiplication but are not 'immune substances in the accepted sense

True Antibodies

In the first group are included various classes of specific antibacterial and antiviral antibodies present in the circulation without evidence of previous infection of the host by these agents In some cases contact with agents having antigens common to these organisms may account for this phenomenon—for example the fairly wide distribution of bactericidal antibody for *Bacillus anthracis* and of precipitating antibody for the polysaccharide of the Type II *Pneumococcus* The presence of circulating antibody for poliomyelitis virus, diphtheria toxin various streptococcal products etc without known prior infection is probably not related to serologic maturation or development of immunity *by a purely physiologic process* There is ample evidence to support the concept that such humoral antibodies are the result of stimulation by clinically inapparent or unrecognized infection Thus, during World War II some of the Pacific Island inhabitants who were thought to have never had diphtheria but were, nevertheless Schick negative reactors, exhibited a high incidence of 'tropical ulcers' which were due

to chronic diphtheritic infection of the skin

Other Serum Components

A serum component which is of significance in recovery from infections due to certain bacteria but which is not an antibody, is complement or alexin This is probably an enzyme and consists of four distinct portions, all of which must be present and active for lysis of bacteria to take place in the presence of amboceptor or bacteriolysin That alexin may on occasion aid in recovery from infection has been demonstrated in the pre chemotherapy era by the improvement in the course of pneumococcal pneumonia or meningococcic meningitis, which failed to respond to specific serum, after the administration of plasma containing adequate quantities of complement

Another serum constituent which may play a role in the general defense against bacterial invasion, particularly by organisms which produce "spreading factor" or hyaluronidase—the *Streptoccus pyogenes* for example—is a naturally occurring anti hyaluronidase Circulating fibrinogen also exerts an effect in protecting against bacterial invasion because its conversion to fibrin at the locus of infection tends to restrict spread of bacteria

While some of the tissue fluids may contain various antibodies particularly after recovery from infection as, for instance the nasal secretions in influenza, in many instances antibacterial, and antiviral activity is not associated with demonstrable antibody

In some tissue fluids the mechanism of bacteriostasis and virostasis is unknown In others, the hydrogen ion concentration is the effective factor In the normal person the high degree of acidity of the gastric juice not only prevents the implantation of some bacteria and viruses but actually kills them It is not effective, however, in completely preventing invasion by way of the gastrointestinal tract since the stomach is the portal of entry for such infections as typhoid fever, the salmonelloses, bacillary and amebic dysentery, and trichinosis

The hydrogen ion concentration of the secretions of the vagina is also an efficient barrier against local implantation of certain organisms Because the vaginal fluid of the menstruating woman has a relatively low *p*H 4 5–6 0, syphilitic chancre of the vagina is rare, the primary lesion tends to occur on the cervix uteri where the secretions are alkaline Gonococcal vulvovaginitis is encountered practically only in the prepubertal and postmenopausal age groups While this has been thought by some to be related to the structure of the vaginal mucous membrane, the lack of acidity probably also plays an important role A *p*H below 6 4 inhibits the growth of the gonococcus, the hydrogen ion concentration of the vaginal secretions of young children and older women is usually above *p*H 6 4

There is a humoral factor in tears which is bacteriolytic This substance *lysozyme* dissolves primarily gram positive, nonpathogenic bacteria There is no evidence that it is active against virulent organisms The free flow of tears probably affords more important protection than lysozyme by removing foreign particles mechanically

Normal cerebrospinal fluid does not support the growth of most pathogenic organisms Whether this is due to a lack of necessary nutritional factors or to the presence of inhibitory substances is not known Purulent exudate, such as occurs in meningitis may introduce materials into the spinal fluid which stimulate bacterial multiplication

ENDOCRINE FACTORS

There is suggestive clinical evidence that various endocrine secretions, or the lack of

them may exert an important influence on resistance to infection

Most of the data in this field have been obtained from the experimental animal It has been shown for instance that increased resistance to tuberculosis follows administration of urinary gonadotropins, that pregnancy decreases susceptibility to syphilitic infection in the rabbit and that various anterior pituitary substances are protective in anthrax

There are a number of situations in clinical medicine in which the endocrine organs appear to play a role in conditioning the response that follows contact with an infectious agent The greatly increased susceptibility to all infections of the person with diabetes mellitus is common knowledge The mechanism of this decreased resistance is however, still unknown It is not due merely to an increased glucose content of the tissues and body fluids since the quantity of carbohydrate available normally is adequate to support maximal bacterial growth It is probably related to a defect in the immune mechanism recent studies suggest that it may reside in an abnormality of the albumin component of the serum

Pregnancy and Menstruation

The alteration in the course of pulmonary tuberculosis by the gravid state is also well known In some instances the disease may get worse in others it may improve In some women a rather benign status present during pregnancy may be dramatically transformed into rapidly advancing tuberculosis after delivery Pregnancy also appears to suppress syphilitic infection The endocrine system probably plays an important role in the development of clinically apparent poliomyelitis in both man and animals Monkeys treated with estrogen are apparently less susceptible to the paralytic form of the disease than untreated controls There is little doubt that pregnancy in the human increases the risk of development of paralytic poliomyelitis Recent studies suggest a relationship between the endocrine changes associated with menstruation and increased susceptibility to this disease

That changes in the secretion of the anterior pituitary hormone may result in decreased resistance is implied by the increase in susceptibility and unfavorable reaction to infectious disease in acromegaly and in Cushing's disease due to basophilic adenoma Acne is thought by some investigators to be associated in part at least, with an endocrine dysfunction The age at which it is prevalent and the response, in some cases to therapy with sex hormones suggests the possibility of such a causal relationship

Adrenal Hormones

The recent discovery and wide clinical application of cortisone and adrenocorticotropic hormone in a large variety of diseases has focused attention on the role of the adrenal secretions in conditioning the response to invasion by infectious agents In the past experimental evidence has indicated that these hormones might be of importance in the inactivation of some bacterial toxins There is little doubt that any infectious disease represents a stress situation which may provoke an adrenal response in the same manner as stress due to any other cause The administration of cortisone or ACTH, however, produces no beneficial effect on the course of an infection that cannot be accounted for completely on the basis of reduction in the degree of tissue reactivity the infectious process itself is completely unaffected. For example patients with pneumococcal bacteremia given cortisone may be afebrile and feeling quite well at a time when the organisms are still circulating in the blood The use of these agents may promote spread of infection during or after the

period of therapy, pulmonary tuberculosis may extend rapidly after cessation of ACTH administration In some experimental viral infections in animals no effect on the course of the disease has been produced by the exhibition of ACTH

Although it is possible that the corticoids may interrupt interaction between antigens and their specific antibodies and thus alter the clinical features of an infectious disease, there is no evidence that they interfere with antibody formation The fact that treatment of infections with adrenal substances is without beneficial effect on the primary process does not necessarily rule out the possibility that normally produced adrenal cortical hormones might not favorably influence this type of disease The role of the adrenal gland in immunity still remains to be elucidated in spite of the demonstration by Dougherty and White of the lympholytic effect and increase in globulin which follows the administration of ACTH these observations have not received full confirmation

HEREDITARY FACTORS

There are no hereditary infectious diseases in man in the sense that living agents capable of invasion are transmitted by way of the germ plasm Nevertheless, certain infections show a tendency to occur with greatly increased or decreased frequency and severity in some families and races The work of Aycock has demonstrated the tendency for paralytic poliomyelitis to appear in certain family groups The tendency of Jewish people to be less susceptible to invasion by and extensive spread of the tubercle bacillus is well known The decreased resistance of the Negro to tuberculosis is also well established The great difference in the reaction to the tubercle bacillus of these two racial groups is probably based on the gradual elimination of the least resistant elements of the Jewish population by centuries of contact, in contrast to the relatively recently acquired contact by the Negro Luria, by selective breeding, produced strains of rabbits with marked variation in susceptibility to experimentally produced tuberculosis

Hereditary factors also have been found operative in other infectious diseases For example, Webster bred one strain of mice highly susceptible to invasion by *S enteritidis* infection and another highly resistant to this organism Hereditary selection of degree of immunity has been demonstrated experimentally with St Louis encephalitis virus *S typhimurium* and *S pullorum* It is interesting that in all instances the change in resistance is specific for only the single organism used in selective breeding and is not the result of a general increase in immunity to all infectious agents

DIETARY FACTORS*

Much has been written in the lay and scientific literature concerning the relationship of lack or abundance of various dietary constituents and susceptibility to infection The well known increase in tuberculosis in times of famine has often been cited as evidence in support of the direct influence of malnutrition on resistance to this disease Unfortunately clear cut evidence that lack of food alone is responsible for the rise in incidence—of tuberculosis and other infectious diseases—is lacking and the situation is often confused by the simultaneous operation of unrelated factors such as crowding poor living conditions, and inadequate control of known active cases It is probable, however that dietary deficiency does play an important role A considerable body of evidence has accumulated in the past few years relating specific constituents of the diet to variations in degree of immunity Much of this information has been obtained from animal experiments too little from observation and study of man

* See also Chapter 32

The ability of the host to elaborate antibody has been related by several investigators to the protein intake and plasma protein level Antibody production is lowered when hypoproteinemia is produced in experimental animals, repletion of protein is associated with an improvement in the immune response

Very little is known concerning the influence of various dietary deficiencies in man on resistance to infection There is no good evidence to indicate that any of the known vitamins act to inhibit infectious processes Patients with disturbance of protein metabolism sufficient to cause low serum albumin have been found to show an appreciable impairment in antibody production In these cases supplementation with lactalbumin or casein preparations may enhance formation of antibodies and partially overcome the subnormal response associated with the hypoalbuminemia this may not always be accompanied by a demonstrable rise in the level of plasma proteins

Balch, on the other hand has recently presented evidence indicating that nutritionally depleted individuals are capable of producing large quantities of antibody This study confirms previous observations that antibody production in man is subject to individual variation The ability to elaborate immune substances however cannot be related to age initial antibody level or total serum protein albumin or globulin levels Balch s study showed that healthy patients on a high protein diet may not produce as much antibody as those who are wasted, dying in negative nitrogen balance, and subsisting on a minimal diet The problem of the relation of protein intake to susceptibility to infection in man, therefore, is unsettled at the moment

AGE AND SEX FACTORS

The increased susceptibility of certain *age groups* to infection is very well known In general the child 3 or 4 years old or younger and the adult 50 years of age or over are less able to resist invasion by infectious agents and are apt to be more ill and to have a poorer prognosis after the disease is established than the older child and young adult The mechanisms responsible for the altered reactivity as related to age is not known, in most instances In others it may be the result of immunization by clinically mild or inapparent infections or of anatomic changes accompanying growth and aging

Children under the age of 2 have practically no resistance to infection by *Hemophilus influenzae* This susceptibility decreases rapidly with increasing age so that it is very uncommon for adults to develop primary disease due to this organism secondary invasion may follow virus infections of the lungs or operations on the head or fractures of the skull, however This difference in immunity to *H influenzae* at various age levels can be correlated with the bactericidal activity of the blood The young child has none of this antibody while the serum of most adults contains large quantities of it

The higher incidence of bronchopneumonia in the older adult may be the result of the slower glottis reflexes characteristic of this age group with consequent greater ease of aspiration of bacteria laden mucus from the pharynx Middle ear infections become less frequent with increasing age, possibly because, with growth, the eustachian tube is altered in position and in size, thus restricting the spread of infection from the throat to the middle ear

In most of the infectious diseases of man, *sex difference* plays little or no role in determining immunity In a few specific situations changes in the economy of the sex hormones may influence resistance to invasion as, for example, the increased prevalence of poliomyelitis in pregnancy, and the decreased susceptibility of the estrogen

treated castrate monkey to this disease In general, however, some of the common viral infections such as mumps, rubeola, *rubella*, and poliomyelitis occur somewhat more frequently in males during childhood, and in females in the older age groups

FACTORS OF CLIMATE AND TEMPERATURE

The influence of climate on resistance to certain infectious diseases may be more apparent than real Careful study has shown that many infections which were thought never to occur in certain areas of the world, actually appear not infrequently *but are often missed because they are* extremely mild or have atypical, unrecognized features The geographical distribution of many of the infectious diseases is in all probability much more a function of the micro-organism than of the host Thus, the decreased incidence of streptococcal infection in the tropics is not due to immunity of the population but rather to the relative scarcity of the organism Likewise, the very low prevalence of malaria in the north temperate zone does not result from a dearth of susceptible hosts, the absence or low incidence of patients with infected blood or scarcity of the proper species of mosquito, or both are responsible

Attempts have been made to relate *changes in temperature*, humidity, and season of the year to alteration in prevalence of some *diseases For example, the* occurrence of poliomyelitis most frequently in the summer has been thought to be due to the lowering of resistance as a result of the failure of the human defense mechanism to adjust to sudden change from cool to warm weather, especially when temperature variation is great There is little evidence to support such an hypothesis Armstrong has recently demonstrated a correlation between absolute humidity and the incidence of *poliomyelitis, he postu*lated that a high degree of humidity produces changes in the nasal mucous membranes and affects the ease of ingress and egress of the virus

Influence of Body Temperature

The effect of body temperature in conditioning the resistance of the host to bacterial invasion has been well known for a very long time Anthrax in birds serves as a good example of this phenomenon Although chickens are ordinarily immune to *infection by Bacillus anthracis, reduction* of their body temperature by chilling makes them highly susceptible This phenomenon is not dependent on the tempera*ture alone* since the organisms *will* grow in vitro at the normal temperature level of the bird *Treponema pallidum* will not produce infection in rabbits maintained at 30° to 35° C warming the animals allows multiplication of the spirochete and invasion to occur

Another outstanding example of the application of this principle in determining host resistance is seen in herpes simplex infection Artificially produced fever may be followed in about half the cases by the appearance of 'fever blisters' This results *from the disruption of a nicely balanced* relationship between the host and the virus, when this symbiosis is undisturbed no harm comes to either the parasite or man, elevation of the temperature tips the balance in favor of the virus and disease *appears*

The febrile response of infections may exert some degree of beneficial effect because defense reactions, humoral or cellular or both may proceed at a more rapid rate within certain limits when the temperature is elevated Chilling may affect susceptibility deleteriously *Monkeys immersed in* cold water appear to develop more extensive paralyses after inoculation with the poliomyelitis virus than control animals infected in the same manner but maintained at 30° C In the human, decreased

resistance following chilling may be related to alteration in the blood supply of the nasal mucosa This may account for the increased risk of upper respiratory tract infection following exposure to cold air Nungester has suggested that the changes in the mucous membrane of the nose that follow chilling result in an increase of mucin secretion and since this material is present in excess, it enhances the virulence of an infecting agent

FATIGUE FACTORS

While it has been postulated that unusual fatigue increases susceptibility to infection, incontrovertible evidence supporting this relationship is lacking Experimental studies of this problem in a wide variety of infections in animals have not yielded conclusive results in many instances There is some evidence that excessive muscular activity during the incubation period or early invasive stage of poliomyelitis may increase the extent of paralysis in both the naturally occurring disease in the human and the experimental infection in monkeys Recently, this phenomenon as it applies to man has been challenged and has been stated to occur, if it does at all, primarily in older adults The entire question of the relationship of fatigue, muscular as well as emotional, to susceptibility to infection is in need of thorough investigation particularly with respect to the so-called stress reactions"

FACTORS OF MICROBIAL ANTAGONISM

As paradoxical as it may appear, normal contamination of certain areas of the body by a heterogeneous bacterial flora may be an important factor in preventing invasion by pathogenic organisms either already present in small numbers or introduced by contact with sick or healthy carriers

The clinical significance of this phenomenon has been brought to light recently by the extensive use of antibiotic therapy A moderate number of "superinfections have been observed which have occurred during the chemotherapy of various infections and which have arisen apparently as a result of changes in the bacterial population normally present on mucous surfaces, particularly the upper respiratory tract. Pneumonia and bacteremia due to *Hemophilus influenzae* have been described in patients receiving penicillin while staphylococcal infections have occurred in some individuals treated with streptomycin or aureomycin Secondary invasion by *Proteus vulgaris, Candida albicans,* or *Torula histolytica* may follow the exhibition of penicillin, aureomycin, chloromycetin, or terramycin In most of these cases the secondarily invading agents are present in very small numbers in the respiratory tract and become predominant only after most or all of the members of the normal bacterial population have been removed by chemotherapy, following this, 'superinfection' occurs

These observations suggest that the flora of the upper respiratory tract—mostly nonpathogenic—exerts a 'blocking' action on the multiplication of the very small number of virulent organisms usually present The use of antibiotics may remove this block by destroying the components of the normal flora and thus allow an increase in the number of the pathogens to the point where they can invade the tissues and produce disease It is possible, however, that superinfections' result from direct stimulation of certain groups of organisms by the antibiotic agent, however, this does not seem very likely in the face of the evidence now available

In a number of situations the antimicrobial activity of the normal bacterial flora is clear cut and can be related to a specific chemical effect For example, during pregnancy the marked preponderance in the vagina of Doderlein's bacillus, causes pro-

duction of large quantities of acid (*p*H 4 5) and discourages implantation of many pathogenic bacteria which cannot live in such an acid environment, thus protecting against some types of puerperal infection Another example of this phenomenon is the recent demonstration that some strains of *Str pyogenes* normally present in the nasopharynx produce a soluble substance which inhibits the growth of the diphtheria bacillus Although inadequately investigated and, for the most part, unproved, the heterogeneous collection of bacteria normally resident in the lower ileum and colon of man may constitute a system of inhibitory mechanisms which prevent infection of the bowel These may act either through the production of a chemical environment inimical to pathogens or possibly through the elaboration of antibiotic substances

II. *Acquired Active Immunity*

NATURAL ACTIVE IMMUNITY

Most of the naturally occurring, nonfatal human infections endow their victims with a variable degree of immunity, in some, resistance to reinvasion by the homologous agent persists with rare exception, for life, in others full susceptibility returns in as short a time as three to four weeks In general diseases produced by bacteria are followed by a low level of resistance while invasion by viruses results in prolonged immunity There are, however, many exceptions to this generalization

Immunity Following Virus Infections

Both extremes of duration of immunity are observed following naturally occurring virus infections Resistance to reinvasion by the agent or agents responsible for the common cold is very short lived and patients may develop repeated attacks three or four or more times in one year, for that matter, one cold may be followed by another in four to five weeks On the other hand, the first episode of yellow fever confers immunity for life

Mechanisms of Antiviral Immunity The mechanisms responsible for such differences in the duration of antiviral immunity has been postulated to involve primarily variations in persistence of viruses in the tissues which they have parasitized Prolonged resistance to reinfection is thought to be related to persistence of virus in the tissues of the recovered individual This hypothesis is supported by the observation that circulating antibodies may be detectable for as long as fifty years after an attack of yellow fever

As Rivers has pointed out this does not mean that an immune person is capable of spreading disease, because it is most likely that the virus is stored in some remote part of the body within living cells where it cannot come in contact with circulating antibodies and from which point it cannot for one reason or another, reach the outside world Thus a virus may reside intracellularly in the host after recovery from infection, be protected from the effect of antibody because of its anatomic location and live in symbiotic relationship with the host for many years It is thought that in addition to yellow fever, this is the basis for the prolonged resistance following measles, rubella poliomyelitis, smallpox chickenpox and the virus encephalitides, among other viral infections in which immunity is of long duration

By inference, in the virus diseases in

which susceptibility returns quickly—such as the common cold and influenza—elimination of the infecting agent from the tissues is assumed to be very rapid Both of these infections involve the relatively superficial layer of the respiratory mucous membrane Because these cells are being exchanged for new ones at a fairly rapid rate in contrast to cells of such organs as the liver or brain the viruses may disappear from the host relatively early and therefore can act as antigenic stimuli only briefly Kunkel in a study of aster yellows in periwinkles has presented evidence in support of the hypothesis that continuing immunity may be related to persistence of virus in cells He showed that following the establishment of disease in these plants it was impossible to produce reinfection with the same virus When however the periwinkles were exposed to a temperature which had no effect on them but killed the virus a new attack of aster yellows could be produced

Antibody and Resistance to Viral Infection Burnet has stressed the development of antibody in relation to overcoming active viral infection and in the subsequent maintenance of resistance

Broadly speaking there are three different situations which may develop (1) Infection may be followed by the elimination of the virus and permanent or at least prolonged immunity (2) Infection persists with repeated opportunities for liberation of the virus despite active antibody production (3) Infection of mucous surfaces is followed by antibody production and immunity of varying duration These three categories are not sharply delimited and intermediate conditions may be recognized

The conditions governing the development of various degrees of resistance to virus disease are considered by Burnet to be the following

As a general rule, solid and prolonged immunity results only when two conditions are fulfilled The first requirement is that the infection must at some stage involve dissemination of virus through the blood stream, providing an effective stimulus to the whole antibody producing mechanism The second condition is that when an opportunity for re infection occurs, the virus must be exposed to circulating antibody before it can reach those cells which when specifically damaged by the virus provoke the characteristic symptoms of clinical infection

Yellow fever is an example of an infection which fulfills both of these requirements Both conditions are probably also met by smallpox, chickenpox measles, and rubella In dengue, however, in spite of the viremia which occurs in the early febrile period, immunity is only transient Quite distinctive are herpes simplex infections which persist despite the presence of circulating antibody Although antiviral activity is demonstrable in the blood within two weeks of the primary infection and apparently remains for life local recrudescences of activity— fever blisters, genital herpes etc—may continue to occur indefinitely, uninfluenced by the presence of the humoral neutralizing substances

Antigen Specificity Of great importance in determining the efficacy of immunity following viral infection are differences in antigenic constitution of the infecting agents Although long lasting resistance usually follows an attack of poliomyelitis this immunity is effective only against strains of the same antigenic composition as the initially infecting one Thus recovery from disease produced by the Lansing type does not confer immunity to invasion by the Brunhilde or Leon viruses It is possible that this phenomenon accounts for the increasing number of reports of second attacks of poliomyelitis particularly in adults The same mechanism is of importance in virus influenza the resistance which follows infection with one

serologic type of virus plays no role in protecting against invasion by another strain which is antigenically distinct

Immunity Following Bacterial Infections

As a rule the immunity which follows most of the naturally occurring bacterial infections is short lived and in some instances may not even reach a degree sufficient to prevent the development of chronicity The presence of agglutinins precipitins or complement fixing antibodies in the serum of patients recovered from a bacterial disease bears little or no relationship to effective resistance to reinfection An illustration of the fact that these types of antibody are insignificant in influencing susceptibility is the relapse in typhoid fever this usually occurs late in the course of the disease when the agglutinin titer is rising rapidly or is already high

Bactericidal Antibodies The antibodies which are most important in determining immunity to bacterial infection are those which kill organisms (bactericidal) and the antitoxins The level of bactericidal activity of the serum for *Hemophilus pertussis* or the *Streptococcus pyogenes* for example can be related in most instances to clinically demonstrable resistance to reinfection The duration of this type of immunity may be quite long but the exact period of persistence is at present unknown in most cases Pertussis appears to confer life long immunity and second attacks are rare The same is true of most instances of typhoid fever and meningococcal infections Bactericidal activity against the *Str pyogenes* is strictly type specific can be correlated with clinical resistance and is detectable in the serum of recovered patients for at least a year With some bacterial diseases immunity lasts for only a relatively short time Repeated infections by the Salmonella group *Neisseria gonorrhoeae* *Pneumococcus* *Staphylococcus* and others are common and may occur in the presence of adequate serum levels of agglutinins or precipitins

Antitoxins Bacterial diseases in which toxins are responsible for many or all of the clinical features are for the most part strongly immunizing and resistance often persists for life Although antibodies which affect the organism itself cannot be demonstrated the quantity of circulating antitoxin is sufficient to afford protection for many years after recovery

This is true in diphtheria second attacks of which are very rare although an immune individual may carry virulent organisms in his pharynx for months he does not develop clinical disease because of an adequate level of circulating antitoxin One outstanding exception to this general principle in the toxic infections is tetanus Many patients who recover from this disease all of the manifestations of which are due to toxin and not to invasion and destruction of tissue are highly susceptible to second attacks For this reason recovery from tetanus must be followed in every case by the usual course of immunization with toxoid

Combined Antibacterial and Antitoxic Resistance When the clinical picture in an infectious disease is produced by both local invasion and general intoxication different degrees of resistance to each of the two components in the syndrome may develop scarlet fever is an example of such a situation Recovery from this disease usually confers life long protection against appearance of a rash on subsequent exposure to erythrogenic toxin On the other hand there is little or no resistance to reinvasion and the development of inflammatory reaction to the *Str pyogenes* at the point of entry of the organism Thus antitoxic immunity after scarlet fever is almost permanent while antibacterial resistance is usually only short lived

Type Specificity The antigenic composition of the organism is just as important a determinant of immunity in the bacterial diseases as it is in the viral ones A good illustration of this phenomenon is re

overy from infections due to *Str pyogenes* f which there are at least 47 antigenically listinct serologic types Disease produced by one type leads to the development of a high titer of bactericidal antibody in the serum and clinical resistance to homologous strains for at least a year in many cases but has no effect on resistance to other types This is the basis for repeated episodes of localized streptococcal disease the organisms involved in the recurrences are usually of different antigenic make up than the initially infecting one

Immunity Following Rickettsial Infections

In typhus fever the immunity that follows recovery is assumed to be complete and of long duration in most cases However resistance is not always permanent a number of well authenticated second and even third attacks have been recorded A most interesting and somewhat unusual occurrence is the development of Brill s disease There is little doubt that this represents a recrudescence of an earlier infection by *Rickettsia prowazeki* Individuals who develop this disease are those who have had classical typhus previously (sometimes as long as twenty five to thirty five years before) and have remained completely free of any manifestations of rickettsial infection in the interval between the two attacks The relationship of the recrudescence to immunity during the latent period and the mechanism of the loss of resistance when Brill s disease occurs is unknown

The serum of patients with epidemic typhus fever contains protective antibodies usually only during the first three weeks of illness Zinsser suggested that effective immunity in typhus depends primarily upon tissue factors During convalescence the blood contains large quantities of opsonin which may persist longer than any other demonstrable immune substance Although many patients who have recovered from typhus fever show no humoral antibodies of significance these may be stimulated to rise to an appreciable titer by the administration of dead *R prowazeki* It is highly probable that immunity in this infection is a function of both humoral and cellular factors

Resistance to reinfection after recovery from Rocky Mountain spotted fever is long lasting in most instances although second attacks have been described In scrub typhus immunity is usually of much shorter duration than in the other rickettsial diseases of man Recurrences although usually mild are not uncommon and may appear within a year of the primary infection Inoculation of living strains of *R tsutsugamushi* into human volunteers recovered from scrub typhus reveals some degree of resistance to homologous strains but very little if any to the heterologous organisms Although detailed studies are not available, immunity following Q fever (*C burneti*) probably persists for a long time

Immunity Following Spirochetal Infections

Syphilis The most important spirochetal disease in the practice of the North American physician is syphilis The significance of the antibody responsible for the complement fixation and precipitating reactions (Wassermann and Kahn tests and all their modifications) in clinical resistance to reinfection in syphilis is debatable there is little evidence however, to support the concept of a direct relation between the level of reagin and actual protection against reinvasion by *Treponema pallidum* Second attacks of syphilis are not uncommon they are usually observed in patients receiving treatment early in the course of the disease and only rarely when therapy is instituted after the spontaneous disappearance of the secondary lesions This clinical observation suggests that the individual treated and cured months after acquiring syphilis may have developed some degree of immunity by that time and that this is sufficient to prevent reinvasion Another possibility is that

late treatment does not eradicate all of the organisms resistance to a second attack, therefore, may merely reflect the persistence of the *original infection*

There seems little doubt at present that the serum of syphilitic man and animals contains substances which are antispirochetal to a varying degree Protection experiments in which serum from people in various stages of the disease was *combined* with virulent strains of *T pallidum* and inoculated into the skin of normal rabbits led Turner and his co workers to the following conclusions

As a group, sera from patients with secondary, latent or tertiary syphilis exerted definite inhibitory effect on the development of syphilitic lesions as compared with sera from nonsyphilitic patients or from the normal pool This effect was manifested by complete suppression of lesions at the site of inoculation of serum spirochete mixtures or by prolongation of the incubation period and by smaller average size of lesions Sera from patients with primary syphilis as a group held a somewhat middle position but in general behaved more like serum from nonsyphilitic persons It is concluded that persons with secondary latent and tertiary syphilis as a group possess *humoral antibodies* which kill, or at least inhibit the multiplication of *Treponema pallidum*, and that these protective antibodies probably play a significant role in acquired immunity to the disease It has not been determined whether these antibodies are identical with antibodies to beef heart antigen evoked by syphilitic infection, but there are certain indications that they are not identical

The serum of patients with syphilis contains a factor which is capable of producing cessation of motility of *T pallidum*, this has been referred to as the immobilizing antibody There is good evidence that this immune substance when present is capable of killing the organisms, although loss of motion and death are not necessarily simultaneous

Other Spirochetal Infections In yaws (*T. pertenue*), one attack usually confers prolonged immunity In experiments in human volunteers, resistance to heterologous strains of the spirochete has been found to develop slowly during the course of the natural disease Within the *first three years, reinoculation may give rise to a modi*fied attack but after a period of ten years the majority of cases of yaws are refractory to reinfection There is considerable evidence to suggest that an individual who is resistant to yaws is also not susceptible to syphilis and vice versa

One attack of rat bite fever due to *Spirillum minus* (sodoku) appears to confer permanent protection which is probably related to the presence of circulating bacteriolytic antibody The immunity following Weil s disease (*Leptospira icterohaemorrhagiae*) is long lasting Fresh blood of recovered patients is capable of lysing the organisms *in vivo* (*Pfeiffer phenomenon*) and in vitro Pinta an essentially cutaneous spirochetal (*T carateum*) disease, resembles syphilis somewhat with respect to clinical immunity although the basis for resistance to reinfection in the late stages of this disorder has not been established

Effect of Chemotherapy on Immune Response Following Infection

The exhibition of effective chemotherapy early in the course of some infectious diseases may result in a decrease in the formation of antibody in large groups of patients the total number who develop an immune reaction may be reduced in those in whom antibody appears, the quantity produced may be much less than is present in untreated cases This depends on several factors (1) the intensity of the infection (2) the time in the disease when the antibiotic is used (3) the dose of chemothera

eutic agent and (4) the duration of herapy

Penicillin In infections of the pharynx ue to *Str pyogenes,* the early administra ion of penicillin reduces to about one fifth he expected number of people who show a ise in the serum content of antistreptolysin r antistreptokinase or both This is par icularly true if the drug is administered very three hours intramuscularly If the ral route is used and especially when the loses are spaced as far apart as eight to welve hours the depression of antibody ormation is much less marked Penicillin also suppresses the development of type pecific bacteriostatic antibody in this type of disease In pneumococcal pneumonia on he other hand the production of type pecific antibody is not interfered with when penicillin is used

Aureomycin Aureomycin may also in hibit the evolution of certain humoral im mune substances Thus cases of strepto occic pharyngitis treated with this agent how a lower than usual incidence and titer of antistreptolysin in spite of persistence of the organisms in the throat Under certain circumstances aureomycin may also suppress antibody formation in rickettsial infections in the experimental animal

All of the available evidence suggests therefore that in certain situations the administration of an antibiotic agent *early* in the course of an infection in quantity large enough to cause rapid eradication of the causative organism may lead to the development of no resistance or to a low level of immunity This may be due to the elimination of the source of antigen so rapidly that it has insufficient time to act as an adequate stimulus to antibody for mation This phenomenon probably has important clinical implications but there are still not many definitive studies on this aspect of the problem There are however suggestions that intensive treatment with such an agent as penicillin may result in failure to develop clinical resistance to in fection and second attacks are now known to occur within a short time of the first in infectious diseases where they were uncom mon or even rare prior to the use of chemotherapy

ARTIFICIAL ACTIVE IMMUNITY

Artificial active immunity may be defined as the resistance to infection which follows the administration (usually parenteral) of living attenuated or dead micro organisms or their products All of the immunization procedures commonly used in clinical prac tice produce this type of immunity The materials which are given for this purpose are referred to collectively as *antigens* and the substances which develop as a result of their use and which are responsible for re duction in susceptibility are called *anti bodies* Both of these terms have already been defined earlier in this chapter

The details of the procedures involved in active immunization will not be pre- sented here they are dealt with in the chap ters devoted to specific disease states else where in this book The discussion will be limited to the general principles which apply in artificial active immunization re- gardless of the type of agent involved

Materials Used to Produce Artificial Active Immunity

The agents used to produce active im munity in man are bacteria and their prod ucts viruses and rickettsiae These agents may be (1) living capable of active multi plication and invasive or (2) living but so attenuated that they are incapable of in vading tissues or (3) completely dead

Vaccination against smallpox is an ex ample of the use of a fully pathogenic, actively multiplying virus to invoke the production of immunity Here advantage is taken of the fact that local inoculation of cowpox virus produces sharply limited relatively benign disease (there is some evi

tinue it, particularly if each of a relatively large number of successive inoculations proved painful to the baby, or she thought they did, (2) the presence of the pertussis organisms may act as a local irritant and, therefore, by exerting the effect of an adjuvant lead to the development of greater degree of immunity to all of the components in the combination than if they had been given singly at different times

Number of and Interval Between Injections in Initial Immunization

In some immunizing procedures one injection suffices to produce an adequate level of resistance Protection against influenza, mumps pneumococcal infections, and smallpox, for example, is accomplished by a single administration of the specific antigenic material When bacterial vaccines and toxoids are used, they are given more than once, as a rule Thus, pertussis and typhoid immunization usually consists of a series of at least three injections The production of immunity against diphtheria and tetanus requires only two doses of toxoid, provided the alum precipitated preparations are used Proper spacing between injections is one of the most important aspects of any immunization procedure Too short or too long an interval may lead to partial failure A period of three to four weeks between inoculations is ideal, although with some diseases (e g typhoid) this may be reduced to as short a time as only seven to ten days without impairing the degree of immune response

Duration of Artificial Active Immunity

The duration of artificially induced active immunity varies considerably for each disease and also in different individuals Resistance against some infections is present for only a relatively short time Vaccination against the influenza virus, mumps and *Pneumococcus* probably is effective for no longer than a single year Immunization against smallpox leads to a varying duration of protection but, on the average, is effective for about five to seven years On the other hand, the administration of yellow fever vaccine endows the recipient with life-long immunity Diphtheria toxoid particularly the alum precipitated preparation successfully immunizes at least 95 per cent of the individuals to whom it is given for two years, resistance probably lasts considerably longer in most cases The initial tetanus immunization is protective for only a short time in most people and booster doses are required at periodic intervals to maintain an effective level of circulating antitoxin

"Booster" Doses

The administration of so called "booster or recall injections represents a procedure of proved value in immunology Once the antibody producing mechanism has been activated by an effective initial immunization the subsequent injection of the same or antigenically related material provokes a rapid rise in antibody to a level well above that present at the time the booster dose is given Very often the titer may even increase to a point beyond that reached at the height of response to the primary inoculations

"Booster doses usually consist of a single injection and at the moment appear most useful in protection against pertussis diphtheria, and tetanus, although they have been used for smallpox for a long time, since re vaccination every five to seven years has been extensively practiced

Booster doses of vaccines or toxoids are usually given for two reasons (1) elevation of the quantity of antibody in the absence of known exposure to infection for the purpose of prolonging already established immunity, and (2) following exposure to an infecting agent in order to activate the mechanisms of resistance so that sufficient antibody may develop during the early in

bation period and multiplication of the cro organisms stops before serious in sion of tissues takes place Such prophy xis is ineffective, however, if the incuba on period of the disease is very short

'Booster' doses have their widest field of plication in the three infections for ich immunization is almost universally acticed In *pertussis*, particularly in chil en vaccinated at a very young age, a ngle injection about one year following e completion of the first series increases e intensity and duration of immunity at time in life when susceptibility is highest id the risk of death greatest In *diphthe a* recall injections are useful both for rolongation of resistance without expo ire as well as for rapid elevation of the rculating antitoxin following contact ith an active case In a person who has een immunized artificially or who has had inically apparent infection, a positive chick test may be rapidly converted to a egative reaction by the application of /50 M L D of diphtheria toxin or 0 1 cc f toxoid endermally

Effective protection against *tetanus* re uires the administration of booster doses f toxoid at periodic intervals Following ompletion of the initial immunization gainst this disease the quantity of anti oxin in the blood frequently falls to a oint well below the protective range in a elatively short time It is imperative, herefore, to give a single recall' dose ibout one year after the primary prophy axis This booster raises the quantity of irculating antibody in a very short time The greater the number of such injections he higher usually is the final level at which intitoxin is stabilized In not a small num oer of cases the repeated administration of toxoid may lead to the development of a iter of antitoxin in the serum sufficiently high to protect against the usual infection without the necessity for taking additional preventive measures

One of the most important problems re lating to the 'booster' dose is the matter of the period of time which may be allowed to elapse between the primary immuniza tion and the administration of a 'recall' injection still capable of provoking a rapid rise in antibody Information pertaining to this subject has been obtained mainly from studies in the prophylaxis of tetanus in which it has recently been noted that even six and probably as long as nine years after the initial series of inoculations a dose of toxoid will still produce elevation of the antitoxin titer in the blood within a rela tively short time In most cases the increase in antibody becomes apparent in about forty eight hours after giving the toxoid

Age at Which Active Artificial Immunity May Be Produced

The concept that the very young human organism is relatively incapable of produc ing antibody even on intensive antigenic stimulation has been disproved during the last few years Studies of immunization against pertussis have demonstrated con clusively that prophylactic efforts in this disease may be initiated in children as young as two months of age and be success ful The same observations have recently been made in regard to diphtheria and tetanus It is important to keep in mind, however, that when immunization is car ried out in the neonatal period, a 'booster dose must be given when the patient is about one year old It is probably best to readminister pertussis tetanus, and diph theria antigens just before the child goes to school

Reactions to Immunization

Untoward reactions to immunization may be divided into four groups (1) local ized noninfectious injury produced by the immunizing material (2) local and systemic infections due to contamination of the antigen by heterologous living bacteria or

viruses (3) generalized, constitutional manifestations, and (4) allergic reactions, involving mainly the nervous system, probably resulting from sensitization to the antigen

Localized Trauma Many of the substances employed in immunization produce swelling and pain at the site of inoculation This is particularly true when bacterial suspensions are used, and is especially common after the administration of pertussis vaccine Alum containing antigens may produce sterile abscesses when deposited in muscle or under the skin The endermal instillation of cowpox vaccine not infrequently is followed by localized inflammation with swelling pain, tenderness lymphangitis and tender, sentinel lymphadenopathy, all of these may be caused by activity of the virus alone and are not necessarily related to secondary bacterial infection of the site of inoculation

Local and Systemic Infections In the past vaccination against smallpox was occasionally followed by the development of tetanus Improvement in the method of harvesting the calf lymph used as the vaccine and careful control of its preparation for clinical application has almost completely eliminated this type of complication More recently, the disastrous consequences of accidental contamination of immunizing materials has been emphasized by the epidemic of hepatitis which followed the administration to members of the armed forces of yellow fever vaccine which contained serum in which the virus of homologous serum jaundice was present Such episodes can be prevented by the exclusion of blood and blood products from the substances used in immunization As a corollary to this the importance of using adequately sterilized syringes and needles in preventing the transmission of hepatitis virus should be stressed

Constitutional Reactions Any type of immunizing agent may produce a constitutional reaction which often starts within a few hours after injection and may last for as long as twenty four to forty eight hours This is particularly common following the use of typhoid and influenza vaccines The symptoms may start with chilliness or frank shaking chills and be followed by fever varying degrees of prostration backache and generalized bone, joint and muscle aching nausea vomiting and diarrhea may also occur Some patients are so ill that they are forced to take to their beds a few make the comment that they would rather have had the infection against which they are being protected than suffer the consequences of the immunization

Allergic Reactions A fortunately rare sequel of immunization is meningomyeloencephalitis or peripheral neuritis of varying severity Such accidents are observed during prophylaxis for rabies (about once in every 2000 immunizations), smallpox (rare in the United States but common in Europe particularly in Holland in the mid 1930 s) and pertussis, they occur very rarely after the injection of typhoid vaccine or tetanus toxoid The mechanism of this disorder of the nervous system is not well understood It is thought by many investigators at present that it may result from a hypersensitivity reaction in which nervous tissue participates most intensely and extensively, this hypothesis has some support in experimental studies in animals The possibility that the immunizing procedure activates a latent virus resident in nervous tissue must also be considered That this phenomenon may be involved in the pathogenesis of postvaccinial encephalitis is suggested by the fact that cowpox vaccine administered to Americans has rarely produced nervous system manifestations while the same material given to the inhabitants of Holland has led to the appearance of a relatively large number of cases Although involvement of the nervous system as a result of immunization is always

ous and sometimes fatal, it is important point out that it is so uncommon that it st not be considered as a contraindica n to routine immunizing practices ept in very unusual circumstances On the other hand, the development of any suggestion of nervous tissue dysfunction during the course of prophylaxis should dictate immediate discontinuation of fur ther injections

III Acquired Passive Immunity

TURAL (CONGENITAL) PASSIVE MUNITY

Many years ago Theobald Smith showed it 75 to 80 per cent of calves failing to eive colostrum succumbed to *E coli* cteremia, whereas animals fed on this terial for only a very short period after th survived The protective effect of this ostance appeared to be related to its con nt of pseudo and euglobulin In man the nsfer of antibody to the fetus takes place ainly across the placental membrane Al ough small amounts of immune bodies ay be present in human colostrum ey have little or no importance in deter ining resistance to infection during the onatal period Studies of the concentra on of diphtheria antitoxin in the serum d milk of women have revealed that it is ways present in much smaller quantities the breast secretion than in the blood d that it disappears from the milk almost mpletely in about ten days

The differences in the antibody content the fetal blood of man and animals are tributable mainly to variation in the ructure of the respective placentas which turn, determines their permeability to arious materials in the maternal circula on The placentas of cows, sheep, horses nd goats do not allow the transfer of rotective substances and these species, herefore must obtain antibodies from co ostrum if they are to be resistant to infec ion in the period shortly after birth In uman beings rabbits, guinea pigs and uce, on the other hand, transplacental passage of various antibodies occurs freely Ingestion of colostrum is therefore, not necessary and the young animals are fully protected against some diseases by the im mune bodies which they get by way of the mother s blood The role of colostrum in protecting the newborn human infant against infection is probably very insignifi cant because the small quantity of anti bodies which it contains usually do not withstand the process of gastrointestinal digestion

The newborn child possesses a strong immunity against measles rubella diph theria poliomyelitis influenza, scarlet fever and *H influenzae* There is no con genitally acquired resistance to *S aureus*, the tetanus bacillus the *Str pyogenes*, the *Salmonellae*, *H pertussis* and the virus of chicken pox among others In most instances, clinical protection can be cor related with demonstrable circulating anti body, in others no such relationship prevails The very young child although highly susceptible to streptococcal infec tions does not develop scarlet fever This is so despite the absence of antitoxin in the blood of both the mother and infant there is no adequate explanation for this phe nomenon The duration of neonatal im munity is variable with measles rubella, scarlet fever and diphtheria, it is about six months

ARTIFICIAL PASSIVE IMMUNITY

Artificial passive immunization may be defined as the production of temporary

immunity to an infectious agent by the administration of serum or gamma globulin containing preformed antibody It is usually carried out after exposure to or actual invasion by micro-organisms or their toxins has occurred Thus, this type of protection may be applied both prophylactically and therapeutically Several types of passively immunizing materials derived from human or animal blood are useful Their content of antibody is the result either of naturally acquired infection (*serum or gamma globulin from patients* convalescent from an infection) or artificial active immunization (antiserum prepared by repeated injections into animals—tetanus or polyvalent gas gangrene antitoxin—or humans—pertussis antiserum)

The use of placental extracts as a source of immune bodies has been almost completely given up because it frequently gave rise to discomforting reactions and because of the availability of more effective materials

Prophylactic Use of Antiserum

Prophylaxis with serum or its products still occupies an important place in clinical practice Gamma globulin obtained from large pools of normal human blood is useful in protecting against infection by the viruses of measles and probably infectious hepatitis *Gamma globulin prepared from the blood of humans* who have had whooping cough and have subsequently been hyperimmunized by the administration of suspensions of dead organisms may be employed successfully for the prevention of pertussis in susceptible children *if administered shortly after exposure* The serum of *horses rarely that of other animals* which have been actively immunized by the injection of toxoid is effective in reducing the incidence of tetanus and diphtheria when given a short time after *contact* with the agents of these diseases

The *quantity* of globulin necessary for protection is relatively small Thus 0 1 cc of human gamma globulin per pound of body weight, if given early enough will completely eliminate, in most instances the development of measles The most important consideration in the prevention of infection by this method is the length of the elapsed interval between exposure and the administration of antibody, *the shorter this* period, the greater is the possibility of producing effective prophylaxis The duration of the incubation period is another significant determinant When it is very short the earliest injection of protective material may not lead to success even when it is as long as two to three weeks prophylaxis must be carried out relatively soon after contact Thus gamma globulin *given later than five days after exposure to* measles may not prevent the disease although it may make it milder, if it occurs There is evidence to suggest that the same phenomenon obtains in infectious hepatitis gamma globulin administered early may eliminate the appearance of this disease *completely, while if it is given later* than ten days following exposure the clinical picture may be ameliorated

At times modification of an infection may be more desirable than its complete prevention In measles for example, this may be accomplished by reducing the quantity of globulin *administered to* 0 02 cc per lb body weight or by giving the immune material late in the incubation period, the first is the preferred procedure because it yields the most predictable results

The duration of *protection following* the administration of preformed antibodies varies with their quantity and source Heterologous serum is effective for a shorter time than homologous material In general the injection of horse serum into man confers passive immunity *for roughly two* weeks, there is a loss of a 50 per cent increment of antibody every twenty four hours On the other hand when human serum is administered to man, increased resistance

may be maintained for as long as a month Obviously the larger the quantity of anti body given, the more prolonged is the protective effect, within certain limits

Therapeutic Use of Antiserum

The development of effective chemotherapeutic agents for many of the important infectious diseases has greatly reduced the necessity for and use of serotherapy There is for example practically no need for the administration of antiserum in pneumococcal meningococcal and *H Influenzae* infections or in scarlet fever The situations in which immune serums are still useful and, in some instances represent the most efficient methods of treatment include snake bites tetanus gas gangrene diphtheria botulism and possibly pertussis

The serums used for therapeutic purposes are mainly derived from animals which have been immunized by repeated injection of the specific antigens Antipertussis antibody is obtained from humans who have recovered from this disease and have subsequently been subjected to artificial active immunization The quantities of serum used in therapy are considerably larger than those employed in the prophylaxis of an infection or intoxication and are doubtless in excess of those actually necessary, the quantitative aspects of this type of treatment are more or less empiric The details regarding dosage of serum in specific infections are discussed elsewhere in this book The principles governing the excretion of therapeutically applied anti body are the same as those that pertain when the material is given prophylactically

Allergic Reactions *Heterologous serums must under no circumstances be injected until tests for hypersensitivity have been carried out* The instillation of 0 1 cc. of the serum endermally or into the conjunctival sac and observation for local reactions after twenty to thirty minutes usually suffices to determine sensitivity A careful inquiry into the presence of any type of allergic disease in the present or past is also of great importance In most adults, even in the absence of a positive history or a reaction in the skin or eye, it probably is safest to give a small initial dose of serum and if no untoward effects are noted after thirty minutes to administer the remainder in four or five equal portions at half hourly intervals

In patients who require serotherapy but are sensitive to the material being used, desensitization must be carried out This is accomplished by starting treatment with a very minute amount (as little as 0 1 cc of a 1 100 000 dilution may be necessary) and increasing it every twenty to thirty minutes until the required quantity has been given *Serum of any kind must never be administered unless a syringe full of 1 1000 dilution of epinephrine solution is close at hand and ready for use*

Purpose of Serotherapy One of the most important features of serotherapy, particularly as it applies to the management of disease due to bacterial toxins, is the fact that once exotoxins are fixed to tissues they cannot be inactivated by specific antiserum regardless of the quantity given This phenomenon emphasizes the futility of trying to alter the clinical changes already present at the time antitoxin is given The primary purpose and effect of serotherapy therefore is to neutralize the toxic materials still free in the blood and tissue fluids and to provide a pool of protective antibody for inactivation of any more toxin that may be formed at the site of infection

Site of Inoculation The site of choice for inoculation of antiserums is intramuscular For prophylactic purposes this is adequate When serum is used therapeutically it is necessary to produce a high level of antibody in the blood rapidly This cannot be accomplished by the intramuscular route alone since it has been shown that when serum is injected into the muscles the maximal quantity is not available in

the circulation until about forty eight hours have elapsed, in spite of the fact that absorption from the intramuscular depot starts promptly It is, therefore, best to administer about 75 per cent of the total dose of serum intramuscularly and, if no reaction occurs in an hour or more, to give the remainder intravenously Such combined therapy has the advantage of allowing an adequate blood level to be attained quickly and at the same time establishing an extravascular pool from which antibody will be absorbed relatively slowly and produce a prolonged effect

Reactions to the Administration of Serum

In spite of careful guarding against the administration of animal serums to individuals known to be sensitive, severe sequelae may develop in patients who, by all tests, appear to be nonallergic to such material Serum reactions may occur at three different intervals after injection and may be of several clinical types

The first and most serious is *anaphylaxis*, this usually supervenes within a few seconds to minutes after inoculation It may lead to instantaneous death without any demonstrable signs or symptoms, this is, fortunately, very rare More often, itching, an urticarial eruption, cough, wheezing, pain in the chest, dyspnea, abdominal pain, nausea, vomiting, marked hypotension, syncope, or collapse in any combination are observed If treated promptly with epinephrine most cases survive

The second type of reaction appears two to five days after giving serum and has been called the *anaphylactoid* reaction or "accelerated serum sickness" Its features are quite like those of ordinary serum sickness, it is differentiated mainly by the fact that it appears relatively early

Classic *serum sickness* still occurs quite frequently The risk of development of this sequel is related roughly to the quantity of serum administered If 10 cc or less are injected the incidence of serum sickness is about 10 per cent, with 75 cc or more it is increased to about 75 per cent Treatment of heterologous serums with acid or proteolytic enzymes 'despeciates' them and reduces the rate of occurrence of serum sickness, the presently available preparations of this type are not completely satisfactory in this respect, however

Serum sickness usually develops in from ten to fifteen days after treatment The clinical syndromes which appear differ markedly in severity and extent but consist of one or more or all of the following features fever, generalized aching, arthralgia or arthritis, maculopapular eruptions, urticaria, diarrhea, abdominal pain, generalized lymphadenopathy, hypotension periorbital edema, and various signs and symptoms of nervous system dysfunction As a rule, all of the manifestations clear in three to five days and leave no residua Rarely, serious or fatal complications may occur, these include myocarditis, meningitis, meningo-encephalitis, myelitis with or without encephalitis, and peripheral neuritis Myocarditis may be detected more frequently than it is suspected clinically if serial electrocardiographic studies are carried out during the course of the illness Any single division or the entire nervous system may become involved, although the incidence of this accident in serotherapy is very low, the death rate is of the order of 15 to 20 per cent The clinical pictures are characterized by their variability The cerebrospinal fluid usually contains an increased number of cells and quantity of protein In spite of occasional reactions, even serious ones, there must be no hesitancy in administering specific antiserum in situations where it is required Chemotherapy has not solved many of the problems in the field of infectious disease, although antibiotics have a definite place in their management, the only truly effective therapeutic measure in diseases like diphtheria, tetanus, snake bite, botulism, and gas gangrene is still highly potent antitoxin

4. Sulfonamides and Antibiotics

CHESTER S. KEEFER

THE development of chemotherapy during the past few years has been one of the miraculous achievements of modern medical research The use of potent specific drugs has changed medical practice and has exerted a profound influence on the lives of those ill with infectious diseases

One of the most interesting aspects of this type of treatment has been the specificity of some of the drugs Another has been the rapidity with which new agents have appeared sometimes to supplement sometimes to replace those already in use Conspicuous in this rapidly changing front have been the sulfonamides

Sulfonamides

FOR many years sulfanilamide has been used as a mordant for dyes and the first preparation to be used successfully in man was one of the azo dyes combined with sulfanilamide (prontosil) It soon became apparent that the sulfonamide was the active anti infective agent Using the basic ring structure of sulfanilamide a large number of sulfonamides were soon synthesized and tested in animals for therapeutic potency and toxicity A few were found to be effective in many diseases and relatively nontoxic in man Some of the more important and useful sulfonamides included sulfapyridine sulfathiazole sulfaguanidine sulfasuxidine sulfathalidine sulfamerazine and sulfadiazine At the present time the most widely used products are sulfadiazine and sulfamerazine and the nonabsorbable sulfonamides such as sulfasuxidine (succinylsulfathiazole) or sulfathalidine

The sulfonamides continue to be extremely useful drugs for the treatment of a variety of infections although they have been largely replaced in the treatment of many bacterial infections by the development of antibiotics such as penicillin, streptomycin aureomycin and chloramphenicol

The sulfonamides have advantages in that they can be taken by mouth are gener

ally readily absorbed from the gastrointestinal tract, and are comparatively cheap They have the disadvantage of producing hypersensitivity and renal damage more often than other anti infective agents such as the antibiotics and some of them are so insoluble that they may cause obstruction of the renal tubules unless large quantities of water and alkali are taken

The sulfonamides that are used most widely for the treatment of systemic infections are sulfamerazine and sulfadiazine The three that are used most often for their local effect in the gastrointestinal tract with minimal absorption are sulfaguanidine succinylsulfathiazole and sulfathalidine

SULFADIAZINE

Sulfadiazine is absorbed from the gastrointestinal tract slowly and incompletely It passes into the tissues and body water slowly but it has been recovered in pleural synovial pericardial peritoneal and edema fluids the tissue concentration being 60–75 per cent of that in the blood plasma About 50 per cent of sulfadiazine in the blood plasma is bound to protein There is no correlation between the binding capacity of blood plasma and clinical effectiveness Since only small amounts of sulfadiazine are conjugated by the tissues (acetylated) it is usually unnecessary to ascertain the total sulfadiazine in the blood The excretion of sulfadiazine by the kidney occurs more slowly than it does with some of the other sulfonamides, so that there is a tendency for it to accumulate in the blood when a regular dosage schedule is employed This must be taken into consideration during treatment

Sulfadiazine occurs in the urine in both the free and the acetylated form Neither form is very soluble so that crystalluria is common The formation of renal calculi is infrequent but every precaution should be taken to keep the urine dilute by giving an adequate amount of fluid

SULFAMERAZINE

Absorption from the gastrointestinal tract is more rapid and more complete with sulfamerazine than with sulfadiazine Excretion takes place in the urine at a slower rate, so that higher concentration of the drug may be found in the blood when dosage schedules are regular Usually the drug can be given every six or eight hours with therapeutic effectiveness About eighty five per cent of sulfamerazine is bound to plasma proteins but this property does not have any effect on the clinical effectiveness of the drug The concentration of sulfamerazine in tissue is 50–75 per cent of that in the blood plasma

Like sulfadiazine, very little sulfamerazine is acetylated in the tissues The tendency toward renal calculus formation is less than with sulfadiazine, and the damage to renal tubules is less Adequate fluid (3000 cc) should be given to all patients

CONCENTRATION AND DOSAGE

When a patient is treated with the sulfonamides, it is desirable to maintain an adequate concentration of the drug in the blood plasma and in the tissues for a sufficient period of time to permit optimum bacteriostatic and bactericidal effects It has not been possible to work out and apply a precise schedule of treatment for every infection that provides information concerning the minimum effective tissue concentration of each sulfonamide There is suggestive evidence that a daily dose of sulfadiazine of 4–6 Gm or a daily dose of sulfamerazine of 2–4 Gm is usually adequate to control most infections With this dosage schedule, and divided doses every four to six or eight hours plasma concentrations of 10 mg per 100 cc can usually be maintained For most practical purposes this should be the minimum concentration of sulfadiazine or sulfamerazine in the plasma In some cases however the concentration may need to be higher depend

ing upon the infection and the response to treatment

When one uses one of the less soluble sulfonamides such as sulfaguanidine, succinylsulfathiazole, or "sulfathalidine," larger amounts are given by mouth The dosage for sulfaguanidine is 24 Gm a day, given in doses of 4 Gm every four hours For succinylsulfathiazole, the dose is 3 5 Gm every four hours, i e 21 Gm a day 'Sulfathalidine is given in 1 Gm doses every four hours, or 6 Gm a day

INDICATIONS FOR THE SULFONAMIDES

Sulfadiazine and sulfamerazine are the drugs of choice for the treatment of all cases of meningococcic meningitis, meningococcic sepsis and bacillary dysentery Sulfapyridine has been effective in controlling dermatitis herpetiformis Sulfaguanidine is very effective in the treatment and prevention of some types of bacillary dysentery and in reducing the bacterial population of the large intestine of patients in preparation for surgical procedures on the large bowel Succinylsulfathiazole and 'sulfathalidine' are equally effective for the same type of preparation

DURATION OF TREATMENT

The only general rule that can be followed concerning the duration of treatment in any disease in which the sulfonamides are employed is to continue the drug until the temperature has reached normal and has remained normal for at least three days The drug should be *stopped abruptly and* the course of the disease followed carefully for signs of relapse

SULFAMYLON "MARFANIL," HOMOSULFANILAMIDE-*p*-AMINOMETHYL BENZENE SULFONAMIDE

This sulfonamide differs from the others in common use in that the amino group is separated from the benzene ring by a methyl group It is about fifty per cent soluble in water While there is considerable overlapping with the other sulfonamides in its bacterial spectrum, it is especially active against certain anaerobic bacteria, such as the clostridia and some of the gram negative organisms that are resistant to other sulfonamides Other features of the drug are that it is bactericidal and that its action is not inhibited in the presence of pus or *p* aminobenzoic acid In the clinic it has been used most extensively for the topical treatment of infected wounds for ocular infections and for acute upper respiratory infections Because it is more soluble than the other sulfonamides, it has been used in combination with other sulfonamides, streptomycin, or urea

Sulfamylon has been given by mouth for the treatment of urinary tract infections but too few cases have been studied to warrant an opinion on this procedure

For ocular and upper respiratory infections a 1 per cent solution has been employed For wound infections a 5 per cent solution in combination with streptomycin 200 units per cc, has been used for the prevention of infection and the treatment of those with infected wounds

There is some evidence that sulfamylon is degraded in the tissues so that this may limit its usefulness in the treatment of systemic infections

In brief, sulfamylon has been used locally in infected wounds It has a positive effect especially against anaerobes (clostridia) *and organisms resistant to penicillin* and streptomycin This is especially striking in infections from *Proteus vulgaris* and *Pseudomonas aeruginosa*

"NISULFADINE" AND "NISULFAZOLE"

"Nisulfadine" and "nisulfazole" are *p*-nitrobenzene sulfonamides In the intestinal tract "nisulfadine" is reduced to sulfa

pyridine and nisulfazole to sulfathiazole These two compounds have been used most often for the treatment of chronic ulcerative colitis Better results have been reported by Major from the use of these sulfonamides than from any other drug It is of considerable interest in this connection that "nisulfadine is the sulfonamide that inhibits the action of lysozyme in the large bowel This may explain in part its activit in ulcerative colitis

SULFACETAMIDE

This agent in 30 per cent solution ha been used most extensively in the treatmen of ocular infections due to both gram negative and gram positive organisms The results have been favorable

Antibiotics

USEFULNESS OF THE ANTIBIOTICS *IN THE TREATMENT OF INFECTIONS*

There is no doubt that the antibiotics have completely revolutionized the treatment of infections Beginning with tyrothricin, which can be used for the treatment of local and superficial infections the number of antibiotics in general use now includes penicillin, streptomycin aureomycin, chloramphenicol bacitracin terramycin and polymyxin It is impossible to assess all the benefits that have followed from the use of these agents, but it is fair to say that many lives have been saved or prolonged, the course of many diseases has been shortened many complications have been prevented and there has been a great alleviation of suffering

SELECTION

The physician is faced every day with the problem of deciding which antibiotic he should use for the treatment of those with infections The various antibiotics that are available have a well-defined antibacterial spectrum, and when there is an overlapping of effects one antibiotic may be superior to another in a specific infection It is essential to know the etiology of the infection if the proper antibiotic is to be selected Each of the antibiotics has a definite field of usefulness and application Some of them are effective against certain species of organisms and ineffective against others Some are highly specific for one group of infections and have little or no effect against others For example, penicillin is most effective against gram positive cocci infections and in gonococcic and *Treponema pallidum* infections whereas it has little or no effect in other gram negative infections Aureomycin is effective in both gram positive and gram negative infections However, it is not as potent as penicillin in the treatment of gram positive bacterial infections, gonorrhea, and syphilis. It is more potent than streptomycin in the treatment of gram negative bacterial infections such as brucellosis In the treatment of rickettsial infections, in primary atypical bronchopneumonia of viral origin and in lymphogranuloma venereum infections aureomycin has a specific effect that cannot be obtained with either penicillin or streptomycin Also it may be of great value in the treatment of such diseases as penicillin resistant infections with *Staphylococcus aureus* and in herpes zoster and granuloma inguinale

Chloramphenicol is more potent against gram negative organisms than it is against gram positive organisms It is highly effec

tive against the typhoid bacillus and against rickettsial diseases, primary atypical pneumonia, undulant fever, urinary tract infections, and lymphogranuloma venereum

CONCENTRATION

The concentration of antibiotics in the tissues and at the site of the infection is of greater importance than the concentration in the plasma When penicillin is given the concentration in the tissues is approximately 25–50 per cent of that in the plasma With chloramphenicol it is 30–50 per cent of the plasma concentration In each case about 50 per cent of the antibiotic in the blood is bound to protein

It is well, then in the treatment of any infection to maintain the plasma concentration at a level that is two to eight times the concentration that is required to inhibit completely the growth of the infecting organism *in vitro*

PENICILLIN

Dosage Forms and Indications

Penicillin continues to be the most extensively used antibiotic agent in medical practice today While there are a number of dosage forms for oral and parenteral and topical use, the commonest ones are (1) crystalline penicillin G for oral use (2) sodium or potassium salts of penicillin G for injection in aqueous solution, (3) procaine penicillin G suspended in water, oil, or oil and aluminum monostearate and (4) combinations of crystalline sodium or potassium penicillin and procaine penicillin for dispensing in an aqueous medium

Until the development of the procaine salt of penicillin the water soluble salts were used most extensively Water soluble salts may be injected continuously by the intravenous or intramuscular route More frequently these salts have been injected intermittently by the intramuscular route When intermittent injections are employed, an attempt is made to inject a sufficient amount at regular intervals throughout the day and night so that penicillin is present in the blood and tissues at all times By some, this type of treatment has been called continuous penicillin therapy

When penicillin is injected intermittently but the injections are spaced in such a way that the drug is not present in the blood and tissues at all times during the twenty four hour period, it has been called discontinuous therapy It is a well-established fact that it is unnecessary to maintain a concentration of penicillin in the blood and tissues throughout the day to obtain optimum therapeutic results Infections vary in their susceptibility to penicillin so that it is not surprising that a wide variety of dosage schedules have proved to be adequate Broadly speaking, it can be said that the objective of treatment should be to bring about recovery from infection in the shortest period of time with the least inconvenience to the patient Every patient with an infection presents an individual problem

The first two matters to be decided when water soluble salts of penicillin are selected for use are the total amount to be injected in the twenty four hour period and the frequency of individual injections

Since the minimum effective therapeutic dose has never been determined for all infections it is impossible to make any precise statements about every susceptible infection During the last few years there has been a general tendency to increase the amount of penicillin with each injection and to increase the interval between injections This is true of the more soluble salts as well as the less soluble salts For example in the treatment of lobar pneumonia with water soluble salts it has been demonstrated that a dosage of 200 000 or 300 000 units injected twice daily is as effective as one of 25 000 units given every three or four hours

Procaine Penicillin G

Procaine penicillin G was developed to *reduce the total number* of injections of *penicillin* that may be required in a twenty four hour period This salt is relatively *insoluble* in water, *but when it is suspended in oil* or water and injected intramuscularly it is absorbed slowly When water is used *for the suspending* agent, a small amount of a detergent is added so that it may be *suspended* evenly Following the injection of 1 cc containing 300,000 units of penicillin, maximum plasma concentrations are reached within one to two hours The concentration then decreases slowly so that in practically all patients the plasma concentration will be above 0 05 unit per cc at the end of twelve hours and in at least eighty per cent of the patients at the end of twenty four hours

The essential differences between plasma concentrations of penicillin when procaine penicillin and crystalline penicillin are compared are as follows Maximum plasma concentrations follow aqueous sodium penicillin G within ten to fifteen minutes after injection they are always greater than following a similar amount of procaine penicillin G, *but penicillin disappears from the* circulating blood much more rapidly because the aqueous sodium penicillin G is absorbed more rapidly The plasma concentration following the injection of 300,000 units of aqueous penicillin is usually about the same at the end of one hour as at the end of twelve hours following the same dose of procaine penicillin

Sodium or potassium penicillin G has been combined with procaine penicillin G to produce an initially high concentration of penicillin as well as a twenty four hour concentration in the plasma One cubic centimeter of aqueous material containing 100 000 units of the crystalline salt is combined with 300 000 units of the procaine salt

Aluminum Monostearate. When procaine penicillin G is suspended in oil and *aluminum monostearate is added the* penicillin is absorbed more slowly and uniformly The initial as well as the maximum *plasma concentrations* of penicillin are lower than when other preparations are used, but plasma concentrations of 0 05 unit per cc are commonly present for a longer period of time than when the aqueous suspension is used For example, following the intramuscular injection of 300 000 units of procaine penicillin G in oil and aluminum monostearate, the plasma concentration at the end of one hour averages 0 25 units This is about one sixth as great (average 1 5 units) as the plasma concentration at the end of one hour following the injection of the same salt without aluminum stearate The plasma concentration does not decrease below 0 05 unit for seventy two to ninety six hours in many cases, and this concentration may be maintained for as long as one hundred and twenty hours

When doses of 600 000 units are injected a relatively constant plasma concentration is maintained at a higher level over a period of four or five days, but the initial plasma concentrations are not commensurately greater Studies with this preparation show that it is exceedingly difficult to obtain a high plasma concentration but that the level obtained can be greatly prolonged These observations also show that procaine penicillin G with aluminum monostearate is released from tissues very slowly when compared with other preparations Following the injection of 300,000 units of procaine penicillin G in water or oil this amount is available to the tissues for a twenty four hour period in a concentration that is usually considered to be adequate for controlling the majority of penicillin sensitive infections Following the injection of 300 000 units of the same salt combined with aluminum stearate this amount of penicillin is available to the tis

sues over a period of seventy two to ninety six hours but the concentration of penicillin is always lower during the first twenty four hours of treatment than when no aluminum monostearate is used

Indications and Dosage It is now established that a single daily injection of procaine penicillin G in oil or water is adequate for the effective treatment of most infections requiring penicillin Larger doses of the order of 600 000 units once or twice daily should be given in infections caused by organisms that are only moderately sensitive to penicillin such as staphylococcic infections and those caused by *Streptococcus viridans*

When the combination of procaine penicillin G in oil and aluminum monostearate is employed the injections may be spaced several days apart This is desirable in ambulatory patients or in mild infections when it is unnecessary to see the patient every day According to the experience of Stollerman Roston and Toharsky infections due to bacteria with a resistance of 0 1 unit or less may be treated with one injection of 3 million units since a plasma concentration of 0 1 units per cc can be maintained for a week following such a dose With hospitalized patients one injection a day of procaine penicillin G in oil or water would seem to be adequate for the treatment of all moderately severe infections

Dosage schedules of procaine penicillin G used with success are shown in Table 1

Oral Penicillin

Penicillin is available for oral administration in the form of either the sodium or potassium salts of crystalline penicillin Some preparations are combined with a buffer for the purpose of increasing the stability of the product, and also to enhance its acid neutralizing capacity when introduced into the stomach However, it has been demonstrated repeatedly that it is not necessary to use a buffered preparation to obtain a satisfactory therapeutic result

More and more patients are receiving penicillin by mouth This is a logical way to give any potent drug provided it is absorbed from the gastrointestinal tract The method is convenient since it decreases nursing care and lessens discomfort, saves the time of physicians and nurses and generally costs the patient no more than other procedures besides producing less hypersensitive reactions What is more important is the fact that the oral route has been shown to be as effective as the parenteral route when adequate doses of penicillin are used The therapeutic results that follow oral therapy are comparable in every way to those following parenteral therapy in pneumococcic pneumonia gonorrhea tonsillitis scarlet fever erysipelas acute otitis media due to hemolytic streptococcus

Table 1 Dosage Schedules with Procaine Penicillin G

Condition	Units	Course of injections: Number	Period
Gonorrhea	300 000	1	
Postoperative	300 000	1	Daily
Pneumococcic pneumonia	300 000	1	Daily, 5–7 days
Prophylactic use	300 000	1	Daily
Puerperium	300 000	1	Daily, 5 days
Staphylococcic infections	300,000–600 000	1–2	Daily 7 14 days
Streptococcic infections of throat	300 000	1	Daily 5–7 days
Subacute bacterial endocarditis	600 000	2	Daily, 6–8 weeks
Tooth extractions	300 000	1	1 hour before extraction
Tonsillectomy	300 000	1	

TABLE 2 DOSAGE SCHEDULES WITH ORAL PENICILLIN

Condition	Units	Period
Gonorrhea	200 000– 500 000	
Hemolytic streptococcus infections	450 000–1,000,000	Daily 5–7 days
Pneumococcic pneumonia		
Adults	600 000–1,000 000	Daily
Infants and children	150 000– 200 000	Daily
Staphylococcic infections of the skin	1,000 000	Daily, 5 days
Vincent's stomatitis	400,000– 600,000	Daily, 3–4 days

Vincent's stomatitis and pharyngitis, and staphylococcic infections of the skin and subcutaneous tissues such as abscesses, carbuncles furuncles and impetigo

In the prophylaxis of gonorrhea it has been shown that one tablet of 250 000 units taken within two hours after exposure will usually prevent infection However, the danger of masking the early signs of syphilis should always be remembered when this prophylactic measure is presented

Dosage Dosage schedules have varied greatly In general it can be said that three to five times the minimum effective parenteral dose of penicillin has been found effective These schedules are summed up in Table 2

Carinamide as an Adjunct Carinamide has been used as an adjunct to penicillin therapy to delay excretion of the latter by the kidney This drug acts by inhibiting the excretion of penicillin by the renal tubules It has been found that when 2–4 Gm of carinamide is given by mouth every three or four hours the plasma concentrations of penicillin are two to thirty two times greater than those obtained when the same amount of penicillin is given intramuscularly with carinamide

This form of combined therapy has been most useful for patients who have infections due to highly resistant organisms such as are seen in occasional cases of subacute bacterial endocarditis or staphylococcic sepsis Thus following a single injection of 500,000 units of penicillin intramuscularly combined with 3 Gm of carinamide orally plasma concentrations varying from 28 to 34 units per cc can be maintained for a three hour period Carinamide has been recommended by Boger and Flippin as a valuable agent when more than 500 000 units are required daily for the treatment of any infection

Inhalation of Crystalline Penicillin G

In an attempt to treat a variety of infections of the respiratory tract, methods have been developed for inhalation of penicillin dust directly into the respiratory passages This method has been used most extensively in the treatment of patients with bronchiectasis and other chronic infections of the respiratory tract Infections of the upper part of the respiratory tract have also been treated in this manner In general it can be said that following the inhalation of 100 000 units of penicillin dust there is good evidence that the penicillin is absorbed Maximum levels in the blood plasma are obtained one hour after inhalation and penicillin can be detected for three to five hours after inhalation Cultures of the nose throat and sputum following such therapy show a decrease in the bacterial population and in particular of the gram positive bacteria Hypersensitive reactions have been reported in 3–6 per cent of patients They are characterized by local reactions in the mouth and throat or at the point where penicillin comes in contact with the skin so that patients complain of stomatitis and irritation of the posterior pharynx and skin Systemic reactions are

infrequent Black tongue occasionally appears but disappears when treatment is discontinued

This form of penicillin therapy is easily available for use in office and home practice It is usually recommended that at least one to three inhalations of 100 000 units of penicillin dust be used daily

Penicillin Troches

This dosage form is used for its local effect in the mouth and throat especially in Vincent s infection and as an adjunct to systemic therapy in hemolytic streptococcic tonsillitis In general, it can be said that systemic treatment of these conditions is always superior to local treatment

Penicillin Ointment

Penicillin is combined with various ointment bases for local application to the skin or conjunctivae These preparations may cause a high incidence of penicillin sensitization

Streptomycin and Dihydrostreptomycin

STREPTOMYCIN is derived from the products of growth of a strain of *Streptomyces griseus* It is active against both gram positive and gram negative organisms as well as the tubercle bacillus The gram negative bacteria are more sensitive to streptomycin than the gram positive organisms and so far streptomycin is the most powerful of all the antibiotics against the tubercle bacillus

Dihydrostreptomycin is a derivative from streptomycin by catalytic hydrogenation It has been used in place of streptomycin because it was believed to produce less neurotoxicity This use now however is more limited as damage to the eighth nerve following dihydrostreptomycin therapy is about as frequent as that following streptomycin therapy provided fully therapeutic doses are used There is also evidence indicating the dihydrostreptomycin is as effective as streptomycin gram for gram in the treatment of tuberculosis and all other infections that are susceptible to the action of streptomycin Also dihydrostreptomycin causes fewer hypersensitive reactions than does streptomycin and many patients who are intolerant to the latter have been able to continue treatment with dihydrostreptomycin

All the salts of streptomycin (hydrochloride sulfate, calcium chloride complex) are biologically active and extremely soluble in water or isotonic sodium chloride They are dispensed as dry sterile powder in airtight rubber capped vials each containing the equivalent of 1 Gm or 2 Gm of streptomycin base

Routes of Administration

There are three routes of administration of streptomycin or dihydrostreptomycin intramuscular topical and oral

Streptomycin is given by mouth when a local effect in the intestinal tract is desired but this route is of no value in the treatment of systemic infections, because very little streptomycin is absorbed from the gastrointestinal tract

For all systemic infections streptomycin should be given intramuscularly In the treatment of meningitis, both intramuscular and intrathecal injections are necessary for optimum results In empyema, intrapleural injections are desirable

Side Reactions

There are two important side reactions to streptomycin hypersensitivity reactions characterized by fever, skin eruptions and

eosinophilia and neurologic disturbances such as vertigo deafness or tinnitus

Hypersensitive Reactions Hypersensitive reactions occur in about 5 per cent of patients who receive streptomycin for two weeks or longer Skin eruptions may be erythematous, urticarial maculopapular, or even hemorrhagic Rashes appear most often between the third and tenth day of treatment, but they may be observed as early as the second day Occasionally they do not occur until after treatment has been stopped In some cases they are transitory and disappear within one to three days in spite of continued treatment in other cases they may last for seven to nine days after treatment is discontinued

When any signs of hypersensitivity appear it is advisable to stop treatment, but if the signs of infection are still present, it may be well to continue with a reduced dosage schedule

Relief from the symptoms of burning and itching accompanying the skin eruptions may be obtained by using one of the potent antihistaminics

Neurologic Reactions Vertigo is common in patients who receive large doses 3 Gm a day for three weeks or longer It is observed most often between the seventeenth and twenty fifth days When small doses are employed i e 0 5–1 Gm daily for five to fourteen days the incidence of vertigo is minimal *Also when 1 Gm is given* daily for six weeks the incidence of vertigo is about 15 to 20 per cent The symptom may be mild or severe It usually persists from one day to two months but in some cases it has lasted six to nine months In 10 per cent of patients with vertigo the symptom is severe and may be accompanied by nausea and vomiting In one half the patients the symptom is moderately severe and in about a third it is negligible The acute symptoms persist for seven to ten days and then gradually subside to such a degree that only an unusual stimulus such as a sudden shaking of the head produces transitory symptoms

Deafness is uncommon but it has been reported when large doses of streptomycin are given when there is an associated renal insufficiency or when there is an associated meningitis The deafness varies tremendously both in degree and in duration When it is transitory, it is often associated with tinnitus This type of deafness is encountered most often in the first week of treatment In other cases the deafness is permanent It may be complete or hearing may be reduced by approximately 50 per cent

Tinnitus occurs in about 5 per cent of cases It usually disappears promptly following the discontinuance of streptomycin

Resistant Infections

There are two striking features of streptomycin and its effect on bacteria first the great variation in the sensitivity of various strains of bacteria to the drug and second the rapidity with which some bacteria acquire resistance to it Different strains of a species of organism may vary tremendously in their sensitivity to streptomycin and following treatment with it organisms appear in foci of infections that cannot be killed by concentrations of streptomycin attainable by the clinical use of the drug Inasmuch as optimum results are usually obtained *with streptomycin within* the first seven to ten days it is desirable to use optimum doses during that time In tuberculosis bacterial resistance is usually delayed thirty to forty two days

Clinical Indications

Streptomycin or dihydrostreptomycin is *the drug of choice for the treatment of* tuberculosis tularemia *Haemophilus influenzae* meningitis urinary tract infections due to gram negative bacilli meningitis due to gram negative bacilli and pneumonia due to *H influenzae* or *Klebsiella pneu*

moniae, and also in patients with mixed infections of the peritoneum The dosage and duration of treatment should be guided by the severity of the infection and the re sponse to treatment Every attempt should be made to obtain optimum results within the first seven to fourteen days of treatment, before streptomycin resistant organisms have appeared

Concentration and Dosage

Following intramuscular injection strep tomycin passes freely into the blood and tissues, and it may be found in the bile, aqueous humor, and peritoneal and pleural fluid Very little diffuses into the cerebro spinal fluid It can be found in the kidney and in pus of soft tissue abscesses following intramuscular injection In all cases the concentration in the tissues is less than that in the blood plasma

Streptomycin is excreted in the urine and in the bile There is no good evidence that it is destroyed in the body At least 60 to 80 per cent of the streptomycin injected intramuscularly may be recovered in the urine within twenty four hours

For intrathecal injection a single injec tion of 25-50 mg every twenty four hours is usually adequate for therapeutic pur poses

Oral Administration

So little streptomycin is absorbed from the gastrointestinal tract that it should not be given by the oral route unless one is anxious to reduce the total number of bac teria in the stools This method of therapy has been used as a prophylactic measure in preparing patients for surgical operations on the large bowel It has been employed also but without much success in the treat ment of local and systemic infections begin ning in the intestine such as typhoid fever and Salmonella infections A dosage of 2-3 Gm a day by mouth may be necessary to reduce the number of bacteria in the stools

Inhalation

Streptomycin can be inhaled in aero solized solutions for the treatment of bronchopulmonary infections due to gram negative bacilli or it may be combined with penicillin when a mixed infection is present Concentrations of 50 mg per cc may be inhaled after the drug has been nebulized so that a total amount of 500 mg in a twenty four-hour period is admin istered Only small amounts of streptomycin are absorbed from the lungs so that very little is detected in the blood plasma and only small amounts may be recovered from the urine

Topical Administration (Wound Infec tions, Ocular Infections, External Otitis)

Solutions of streptomycin containing 25-50 mg per cc may be used locally in the conjunctival sac for infections of the con junctiva or cornea The same solutions may be used in the treatment of external otitis due to gram negative organisms There is always however the risk of causing sen sitization to the drug

Intrapleural or Intraperitoneal Injection

A solution of 0 5-1 Gm of strepto mycin in 20-50 cc of sterile isotonic solu tion of sodium chloride may be injected directly into the pleural or peritoneal cavi ties These injections may be repeated every twelve or twenty four hours

Irrigations are ineffective

AUREOMYCIN

Aureomycin is an antibiotic derived from the fermentation of *Streptomyces aureofaciens* It is a golden yellow powder that is stable at room temperature in the dry state It is a weakly basic compound that is prac tically insoluble in water but it is *more* soluble in an alkaline solution of *p*H 8 5 or acid solutions of *p*H 2 9 Aureomycin has not been synthesized It is said to contain carbon nitrogen, oxygen and non ionic

chlorine, but it is distinct from chloramphenicol, which also contains non ionic chlorine

Stability

In dry crystalline form aureomycin is stable at room temperature It loses activity rapidly in dilute neutral or alkaline solutions and in body fluids when they are kept at room or incubator temperature When kept at 5° C, stability is lost more slowly

Absorption and Excretion

Following a single oral dose of aureomycin maximum plasma concentrations are formed within two to four hours and are maintained at a level varying from 5 to 20 μg per cc of plasma when 1 Gm is given every four to six hours Aureomycin begins to appear in the urine within an hour and reaches maximum concentration in two to eight hours, excretion continues for twenty four hours Small amounts have been found in the cerebrospinal fluid following oral administration

Bacterial Spectrum

Aureomycin is active against a wide variety of bacteria, of the gram positive as well as the gram negative group Its activity is greater against coccal organisms than it is against gram negative bacilli but the drug is highly active against Haemophilus organisms *Pseudomonas aeruginosa* and *Proteus vulgaris* appear to be the most resistant of all the bacterial pathogens

The activity of aureomycin against gram positive and gram negative cocci is definitely less than that of penicillin when compared on a weight basis It is about the same for gram negative bacilli as that of streptomycin There is one point, however, that is exceedingly important the activity of aureomycin against any given strain of bacteria is entirely independent of the organism s resistance or sensitivity to any of the other antibiotics

In addition, aureomycin is highly active against rickettsia the viruses of psittacosis, and the lymphogranuloma venereum group, both in embryonated eggs and in experimental animals

Clinical Results

The most impressive clinical results have been observed in patients with rickettsial diseases, primary atypical pneumonia, brucellosis lymphogranuloma venereum, acute peritonitis bacterial pneumonia, penicillin *resistant staphylococcic infections, penicil*lin and streptomycin resistant urinary tract infections, amebiasis and granuloma inguinale The results in typhoid fever and Salmonella infections have been equivocal and disappointing

A variety of other infections have been treated with favorable responses, but too few cases have been recorded to permit a definition of the place of the drug Diseases treated with aureomycin include syphilis, meningococcic sepsis, bacterial meningitis, tularemia, nonspecific urethritis herpes zoster, and herpes simplex

Aureomycin has not influenced pulmonary tuberculosis

Rickettsial Infections There is well established evidence that aureomycin is a highly effective agent in the treatment of *rickettsial diseases including scrub typhus,* murine typhus Q fever (acute cases), recurrent epidemic typhus (Brill s disease) and Rocky Mountain spotted fever Its use for other rickettsial diseases requires additional study Clinical improvement is usually evident within twenty four hours after starting treatment by mouth The temperature commonly returns to normal within seventy two hours and the skin rashes of typhus or Rocky Mountain spotted fever fade within that time

The dosage schedule has been 1 Gm every four to six hours until definite improvement has occurred and 0 5 Gm every six hours thereafter

Primary Atypical (Virus) Pneumonia Aureomycin favorably influences many cases of primary atypical (virus) pneumonia Symptoms improve greatly during the first twenty four hours and the fever subsides within twelve to forty eight hours The recommended dosage is *1 Gm every four to* six hours for twenty four hours and then 0 5 Gm every six hours for at least forty eight hours after the temperature has returned to normal

Bacterial Pneumonias Bacterial pneumonias caused by the pneumococcus respond favorably to aureomycin Favorable responses have also been recorded in a few cases of pneumonia caused by *Haemophilus influenzae* hemolytic streptococci and staphylococci The observations have been made in infants children and adults

Brucellosis Aureomycin is more effective in the treatment of brucellosis than either streptomycin or sulfadiazine The results have been favorable in the sense that the duration of the febrile attack is shortened and the relapse rate is decreased In infections due to *Brucella abortus suis* and *melitensis* the drug seems to be equally effective The recommended dosage schedule is 4-6 Gm a day for a minimal period of two weeks

Lymphogranuloma Venereum The effects of aureomycin in lymphogranuloma venereum have been striking and it should be used in all acute cases In the chronic cases aureomycin has not been so effective This may be due to the chronic changes in the tissues

Staphylococcic Infections *Aureomycin* has proved to be effective in the treatment of some staphylococcic infections that are resistant to penicillin These include staphylococcic bacteremia staphylococcic pneumonia and chronic infections of the skin also secondary infections in chronic pneumonia in children with pulmonary fibrosis of the lungs Certainly in all conditions in which penicillin is usually the drug of choice but in which resistance to it develops aureomycin should be tried

Urinary Tract Infections Aureomycin has been used in a variety of urinary tract infections due to gram negative organisms occurring singly or as multiple infections *Proteus and pyocyaneus organisms* are completely resistant to therapy Bacilli are eliminated from the urine in many cases that have resisted treatment with the sulfonamides and streptomycin As with all other forms of chemotherapy in urinary tract infections the improvement is temporary when there are calculi or other obstructive lesions in the genitourinary tract Occasionally the combination of streptomycin and aureomycin has proved effective in eliminating bacilluria and pyuria when previous therapy given separately has failed Aureomycin is active in an acid medium, and this should be remembered since streptomycin is most active in an alkaline medium

Acute Peritonitis. One of the disorders in which aureomycin has been used successfully is acute generalized peritonitis following perforation of a hollow viscus such as a perforated peptic ulcer or perforated appendix It has been employed both for the treatment of established peritonitis and as a prophylactic agent in some patients who have had perforation of a peptic ulcer but have shown no signs of a generalized peritonitis following operation The bacterial content of the large bowel drops rapidly and remains low for a long period following oral administration As a result *of these observations aureomycin has been* used as a prophylactic agent in preparing patients for abdominal surgery in which the peritoneum is likely to be contaminated and particularly in operations on the large intestine

Infections of the Eye A large number of ocular infections have been treated with aureomycin by the instillation of the borate salt in 0 5 per cent solution into the con

junctival sac. Also ointment is now available for local application in similar infections. Reports show that a wide variety of bacterial agents that infect the conjunctivae respond to aureomycin treatment. The results have been encouraging also in follicular conjunctivitis of unknown cause and in trachoma. In epidemic keratoconjunctivitis they have been irregular. A few patients with dendritic keratitis have responded favorably and the same is true of the uveitis due to a generalized lymphogranuloma venereum infection. The studies of Braley and Sanders record a wide variety of disorders of the eye that might well be influenced favorably by aureomycin.

Miscellaneous Diseases. Isolated cases of meningococcemia have shown rapid improvement following the administration of aureomycin. In acute gonorrhea in men the results have been favorable, but they are not nearly so dramatic as those that follow the use of penicillin. Tularemia, granuloma inguinale, nonspecific urethritis, psittacosis and pertussis have been improved. Amebiasis responds favorably, but amebic hepatitis has failed to respond. A definite antispirochetal effect and the healing of the lesions of syphilis has been reported.

Side Effects

The side effects of aureomycin have been confined almost exclusively to the gastrointestinal tract. Irritation of the tongue and buccal mucosa, nausea, vomiting and diarrhea are the commonest undesirable effects. They usually disappear promptly following discontinuance of the drug.

CHLORAMPHENICOL

Chloramphenicol is a pure crystalline chemical compound that was first produced by fermentation from *Streptomyces venezuelae*. Later it was produced synthetically by the chemists of Parke Davis and Company. It is the first antibiotic to be produced in large quantities by chemical synthesis and is the first product of nature that has been found to contain a nitro group and a dichloracetic acid residue with nonionic chlorine.

Characteristics and Stability

Chloramphenicol is a white neutral crystalline powder which is stable in the dry state. In solutions over a range of *p*H of 2 to 9 it is stable at room temperature for at least twenty-four hours. It is extremely insoluble in water, approximately 0.25 per cent at room temperature, but it is soluble in propylene glycol up to 15 per cent.

The chemical can be determined quantitatively by either the microbiologic assay method using *Shigella paradysenteriae* as the test organism or by the chemical method. In the microbiologic assay method, the active form of the drug is determined. By the chemical method, the total drug, active and inactive, is measured.

Chloramphenicol is administered by mouth.

Absorption and Excretion Following Oral Administration

Following the exhibition of chloramphenicol by mouth, it is absorbed rapidly from the gastrointestinal tract. After a single dose the highest plasma concentrations of the active form of the drug are obtained within two hours. There is a gradual decrease over a period of eight hours and none of the drug is present at the end of twenty-four hours. The plasma concentrations are related to the dosage so that following the administration of 1 Gm., the concentrations vary from 6 to 12 μg per cc. at the end of two hours and decrease to less than 1 μg at the end of eight hours.

There is good evidence that chloramphenicol is excreted in the bile and the urine. Small amounts diffuse into the cerebrospinal fluid.

When the urine is examined following

oral administration appreciable amounts of chloramphenicol are found within one half hour, but maximum concentrations are not found for two to eight hours

It should be pointed out that there is evidence that most of the chloramphenicol absorbed from the gastrointestinal tract is degraded by the liver before it is excreted by the kidney Only about 3 5–8 7 per cent of the amount administered is recovered in the urine as the active form of the drug Chemical studies of the urine show however that between 80 and 92 per cent of the total administered is excreted in twenty four hours Fortunately the concentration of this drug in the urine following 1 or 2 Gm doses is usually high enough to inhibit the growth of susceptible bacteria

Bacterial Spectrum

A large number of organisms are susceptible to the action of chloramphenicol The positive effect is mainly among the gram negative bacteria In this respect it resembles streptomycin With many gram negative organisms however the drug is more active than streptomycin It is about one tenth as active as the latter against the tubercle bacillus

One of the outstanding characteristics of chloramphenicol is its remarkable anti rickettsial potency in embryonated eggs and in mice This carries over to man Some degree of activity has been demonstrated in psittacosis lymphogranuloma venereum and Newcastle s disease The drug has proved ineffective against viruses of type A influenza St Louis and Japanese encephalitis fixed rabies virus and variola

Brucellosis Woodward and his associates report their results in 6 patients Five of them had positive cultures recovered and were followed from three to six months without relapse when they received treatment with chloramphenicol for six to twelve days in amounts varying from 11 25 to 19 25 Gm The average duration of fever varied from two to four days after treatment was started

Rickettsial Diseases Chloramphenicol has been used with striking success in patients with scrub typhus murine typhus Rocky Mountain spotted fever and epidemic typhus Other forms of rickettsial diseases are under investigation Dosage schedules have varied greatly and continue to remain an experimental stage Successful results have been obtained with 1 5 Gm once a day for three days and with 5–6 Gm given over a period of twelve to eighteen hours In some cases an initial dose of 50 mg per kg of body weight has been given and then followed by 0 2–0 3 Gm every two or four hours for a variable period of time

In brief, one must be guided in treatment by the clinical course of the disease An initial dose of 50–75 mg per kg body weight followed by 0 25 Gm every three hours until the temperature has been normal for forty eight hours would appear to be adequate for example for a 60 kg man 3–4 Gm as an initial dose followed by 2 Gm a day

Typhoid Fever The response to chloramphenicol of patients with typhoid fever has been striking The course of the disease has been shortened but the risks of hemorrhage and perforation or relapse have not been entirely removed Revision in the dosage schedule will affect the complications and the relapse rate

Present dosage schedules have included an initial dose of 50 mg per kg body weight, followed by 0 25 Gm every two hours until the temperature has returned to normal and repeated every three to four hours for five days In order to determine whether the relapse rate can be reduced it has been suggested that treatment be continued through the first twenty-one days of the disease since it is well established that most patients who have a true

relapse usually show signs of it within fourteen days after the temperature has returned to normal In some patients with typhoid fever, the temperature has returned to normal within forty eight to seventy two hours of treatment The dosage schedule then might be an initial dose of 3 Gm followed by 3 Gm a day in divided doses every two hours until the temperature has returned to normal, and then 1 5 Gm a day in divided doses every four hours for a variable period of time depending on the response of the patient and course of disease Usually two weeks of continued treatment is adequate to prevent relapses

Primary Atypical Pneumonia The response of primary atypical pneumonia has been favorable when 0 5 Gm is given every two hours for six doses (3 Gm) and then continued with 2 Gm a day given in four divided doses (0 5 Gm every six hours) Treatment has usually been continued for three to five days after the temperature has returned to normal

Urinary Tract Infections A number of micro organisms that cause urinary tract infections are susceptible to chloramphenicol but resistant to streptomycin These include *Escherichia coli*, *Aerobacter aerogenes*, *Proteus vulgaris*, Klebsiella and *Salmonella schottmuelleri* It is well to use the drug in urinary tract infections with an initial dose of 1 Gm, followed by 1 Gm a day for ten days

Miscellaneous Infections Favorable results have been reported in cases of lymphogranuloma venereum and granuloma inguinale, and also in amoebiasis, tularemia, pertussis, and pneumococcic and other bacterial pneumonias

Bacterial Resistance

Bacteria develop resistance to chloramphenicol slowly if at all, so that prolonged treatment can be carried out without great risk of sensitivity

Hypersensitivity

Up to the present time no cases of hypersensitivity to chloramphenicol have been reported

Side Effects

Side effects are infrequent Lower abdominal cramps occur in 5 to 8 per cent of patients Coolness and mottling of the skin of the extremities and weakness in the legs are occasional complaints after several days of treatment No deleterious effects on the liver, or kidneys have been reported One feature noted after several days of treatment is stomatitis and sore throat This is due to monilia infection that appears after the suppression of bacterial growth in the pharynx

One of the undesirable side effects of cloramphenicol is the development in rare instances of some form of blood dyscrasia such as agranulocytosis thrombocytopenic purpura, or aplastic anemia The frequency and the mechanism causing these blood dyscrasias are unknown From the reported cases blood dyscrasias have occurred when the drug has been given for a prolonged period of time or after it has been given repeatedly In a few patients the blood disorder has appeared after a few days' treatment All patients receiving the drug should be followed carefully, and the blood examined at regular intervals for any signs of significant change

POLYMYXIN ("AEROSPORIN")

Polymyxin (aerosporin) is derived from *Bacillus aerosporus and is probably closely* related to the antibiotic obtained from *B polymyxa* It is not a pure substance, since several active fractions can be obtained from the crude preparations They are known as 'aerosporin A, B, and C and these differ from polymyxin This antibiotic is highly selective against gram negative bacilli It is bactericidal in action and is capable of protecting infected animals Re

sistant strains do not appear after prolonged treatment

It is not absorbed from the bowel, from which it eliminates sensitive organisms Following parenteral use it disappears from the blood quickly It does not pass into the cerebrospinal fluid and it is not detected in the bile or in the urine in biologically active form The great drawback to the use of polymyxin or aerosporin has been due to the presence of an antidiuretic principle and a substance which damages the renal tubules The antidiuretic principle has not been detected in man and some purified samples have been free of the renal damaging factor

Clinical trials with polymyxin have been limited owing to the presence of the renal damaging factor However impressive results have been obtained in *Pseudomonas aeruginosa* bacteremia and in meningitis due to the same organism One injection intrathecally daily is adequate for therapeutic concentrations Pertussis has been shortened by treatment

Polymyxin B deserves further clinical trial especially in *Ps aeruginosa* infections and in gram negative bacillary infections

BACITRACIN

Bacitracin was first described by Johnson Anker and Meleney It was derived from a strain of *Bacillus subtilis* that was isolated from a wound This agent has been tested widely in a variety of infections both local and systemic The bacterial spectrum of antibacterial activity is broad and in general resembles that of penicillin in that the drug is more active against gram positive organisms than gram negative ones

Bacitracin is readily soluble in water or physiologic saline and it has been administered systemically by dissolving it in 2 per cent novocaine in physiologic saline

So far bacitracin has been used most effectively in the treatment of wounds and various types of sepsis due to organisms that are resistant to penicillin, streptomycin and the sulfonamides Inasmuch as an increasing number of such cases are constantly appearing it is well to be familiar with this agent

Very little bacitracin is absorbed from the gastrointestinal tract, although it inhibits the growth of many bacteria in the bowel, including clostridia and gram positive cocci Following intramuscular injection, bacitracin appears in the blood and tissues, although very little diffuses into the cerebrospinal fluid It has a low renal clearance which approximates the glomerular filtration rate in contrast to penicillin which has a renal clearance approximating the total renal plasma flow Bacitracin is excreted more slowly than penicillin the rate of excretion remaining at a reasonably constant level for several hours The plasma concentration falls more slowly than does that of penicillin G

Doses varying from 3000 to 50 000 units every six hours have been given for the treatment of systemic infections and they have been well tolerated The one limiting factor in the use of bacitracin for the treatment of systemic infections is the risk of producing renal damage With some preparations this risk has been minimal but with others it is considerable It is well then to exercise caution in using bacitracin systemically and to follow the urine for abnormalities as well as the blood for nitrogen retention

Clinical Applications

Bacitracin has been most effective in infected wounds and other surgical infections in which the organisms are resistant to penicillin and streptomycin In at least seventy per cent of these cases the results have been highly satisfactory Pneumococcic pneumonia, amebiasis pyodermias and ocular infections due to gram positive organisms have responded well Eagle has

shown that bacitracin has an antitrepo nemocidal effect and that it is synergistic with penicillin in the treatment of rabbit syphilis

For ocular and dermatologic infections, the local application of solutions or oint ments is recommended

It seems clear from all the reports that bacitracin has a definite place in antibiotic therapy and that it can be used with perfect safety for the treatment of local infections Also in penicillin and streptomycin resis tant systemic infections that threaten life, it is an extremely useful agent Precautions against renal damage should be taken

TERRAMYCIN

This antibiotic belongs to the so-called broad spectrum anti infective agents and is derived from a species of streptomyces, *Streptomyces rimosus* It is very stable, and in the dry state it shows no detectable loss in activity on prolonged storage at 25° C

Absorption and Excretion

Terramycin is rapidly absorbed from the gastrointestinal tract and produces signifi cant, continuous blood plasma concentra tions with dosages as low as 0 25 Gm every six hours Excretion of terramycin in active form occurs readily in the urine, and at a more rapid rate than either aureomycin or chloramphenicol when these two drugs are given in comparable doses Also relatively large amounts are excreted in the stools Following absorption from the gastroin testinal tract the antibiotic can be found in many organs of the body, including the skin, liver, spinal and pleural fluid, kidney, lungs spleen, and in the bile From a study of the plasma concentration of terramycin following oral administration it would ap pear that optimum concentrations occur within six hours, so it would seem desirable to divide the daily dose into four equal parts

Dosage Forms

The most commonly used dosage form of terramycin is the capsule of crystalline terramycin hydrochloride They are dis pensed in 50, 100, and 250 mg capsules Other available preparations include crys talline terramycin hydrochloride—elixir, oral drops, ophthalmic solution, ophthal mic ointment, topical ointment, troches, and vials containing 0 25 or 0 5 Gm for intravenous use

The capsules are used most widely, since they are convenient and the absorption from the gastrointestinal tract is rapid Intravenous injection of terramycin should be reserved for those patients who are ex tremely ill, and who are unable to take the agent by mouth The solutions of terra mycin have been properly buffered and in no circumstances should aqueous unbuf fered solutions be used for any purpose The acid reaction of terramycin, *p*H 2 5 is responsible for its irritating effects when used locally without buffering

Bacterial Spectrum

It has been demonstrated that terramycin is active both in vitro and in vivo against a wide variety of pathogenic organisms be longing to the bacterial, spirochetal and rickettsial groups, certain of the large viruses and against *E histolytica* Terra mycin acts promptly upon sensitive cells and exerts a *bactericidal* effect when the ratio of the concentration of the antibiotic to the initial number of organisms is high When this ratio diminishes, the bactericidal effect diminishes and a bacteriostatic action only may be shown Hobby has pointed out an additional important fact—that under conditions suitable for bacteriostasis there is a prolonged lag period during which no antimicrobial action is apparent Such studies suggest that when terramycin is used the concentration of the drug in the tissues should be sufficiently high, so that bactericidal effects are produced

From the initial studies of terramycin concerning its action against microbes it was soon designated as an antibiotic with a broad bacterial spectrum suggesting that it was an effective agent against many different species of aerobic and anaerobic micro organisms—gram positive and gram negative organisms spirochetal and rickettsial infections *Endameba histolytica* infections and lymphogranuloma venereum as well as granuloma inguinale and primary atypical pneumonia *Proteus vulgaris* is completely resistant Gram positive cocci are more sensitive to terramycin than gram negative bacilli In this respect the agent resembles aureomycin and penicillin

Side Reactions

There are several symptoms and signs suggesting toxic side reactions The three common ones are nausea vomiting and diarrhea Other less frequent symptoms and signs are stomatitis a skin eruption or epigastric pain The most disturbing side effects are the gastrointestinal symptoms In a few patients the symptoms are so severe that it is necessary to discontinue the drug In others they are of a mild nature and the drug can be continued. In a few cases a new infection due to monilia may appear in the mouth throat, intestinal tract and vagina The only control for such new infections at present is to discontinue the antibiotic.

Choice of Sulfonamides and Antibiotics

AS A guide in the selection of either sulfonamides or antibiotics in the treatment of different infections Table 3 has been made The positive grades are from + to ++++ plus Four plus indicates an effective drug and the one of choice When more than one drug has the same rating there is evidence that each drug has a similar effect A three plus rating indicates that the drug is effective but less so than a four plus rating A one or two plus rating indicates that the drug has a minimum effect but is usually not used alone Obviously such a chart can provide one with only a rough guide in the selection of drugs but it may prove to be useful Some comments are desirable in connection with each condition outlined

In the treatment of *actinomycosis* it has been shown that penicillin and sulfadiazine given in combination are more effective than either one given alone In this disease then both agents should be used together in full therapeutic doses

Aureomycin chloramphenicol and bacitracin given by mouth will control *amebae* in the gastrointestinal tract All of them are useful agents in the treatment of this disease

In anthrax penicillin is the drug of choice although in a few reported cases, streptomycin has controlled infections

Bacterial endocarditis presents many special problems For the common organisms nonhemolytic streptococci and enterococci the treatment of choice is penicillin Enterococcic endocarditis will require massive doses of penicillin and streptomycin as well The amount of each required will depend upon the sensitivity of the organism In a few cases aureomycin and even bacitracin have been used in cases resistant to penicillin and streptomycin For the treatment of staphylococcic, hemolytic streptococcic, pneumococcic meningococcic and gonococcic endocarditis penicillin is the drug of choice. In view of the seriousness of these types of endocarditis, it is

TABLE 3 INDICATED CHEMOTHERAPEUTIC AGENTS

Disease	*Aureomycin*	*Bacitracin*	*Chloramphenicol*	*Penicillin*	*Polymyxin*	*Streptomycin*	*Sulfonamides*
Actinomycosis	–		–	++++		–	+++
Amoebiasis	++++	++++	++++	–	–	–	–
Anthrax	–		–	++++		++	–
Bacterial endocarditis							
Aerobacter aerogenes	+		+	–		+++	+
Enterococcus	–		–	++++		+++	–
Esch coli	+		+	–		++++	–
Gonococcus	–		–	++++		–	–
H influenzae	++			–		++++	++
Klebsiella pneumoniae	–		–	–		++++	–
Meningococcus	++		–	+++		–	++++
Pneumococcus	–		–	++++		–	+++
Ps aeruginosa	–		–	–		++++	–
Staphylococcus	++		–	++++		–	++
Streptobacillus moniliformis	–		–	++++		–	–
Streptococcus anaerobic	–		–	++++		–	–
Streptococcus, nonhemolytic	++		–	++++		++	++
Brucellosis	++++		++++	–		+++	+++
Clostridial infections	–		–	++++		–	+++
Diphtheria	–		–	++++		–	–
Fusospirochaetal infections	–		–	++++		–	–
Gonococcic infections	++		?	++++		+	+++
Gram positive infections	+++	+++	++	++++	–	+	+++
Gram negative infections	++	–	+++	+	++++	++++	+++
Granuloma inguinale	++++		+++	–		++++	–
Herpes simplex	++		–	–		–	–
Herpes zoster	++++		–	–		–	–
Lymphogranuloma venereum	++++		++++	–			++
Meningitis							
Esch coli	–		–	–		++++	+
H influenzae	–		–	–		++++	++
Kb penumoniae	–		–	–		++++	–
Meningococcus	++		–	+++		–	++++
Pneumococcus	++		–	++++		–	+++
Proteus vulgaris	–		–	–		++++	++
Ps aeruginosa	–		–	–	+++	++++	+++

well to combine penicillin with sulfonamides When rare cases of bacterial endocarditis due to gram negative bacilli are encountered streptomycin is the drug of choice It is possible that aureomycin may also be of assistance in these cases

Brucellosis is brought under control with aureomycin chloramphenicol, or with combined treatment of streptomycin and sulfadiazine As far as the evidence goes at present the first two forms of treatment are equally effective and more certain than the third

Gas gangrene requires both penicillin and the sulfonamides systemically, antitoxin, and good surgical treatment Sulfamylon has been used locally in the treatment of wounds containing clostridia

Penicillin can be used in treating *diphtheria bacillus* carriers For the treatment of diphtheria, penicillin may be used when it is combined with antitoxin The combined treatment results in fewer carriers following the acute disease

For *fusospirochetal disease, Vincent's angina*, penicillin is the drug of choice and the same is true for all gonococcic infections

Granuloma inguinale has responded well to streptomycin aureomycin, and chloram

TABLE 3—*Continued*

Disease	*Aureomycin*	*Bacitracin*	*Chloramphenicol*	*Penicillin*	*Polymyxin*	*Streptomycin*	*Sulfonamides*
Meningitis (*continued*)							
Staphylococcus	+++	++	–	++++		++	++
Streptococcus	–		–	++++		–	++++
Tuberculosis	–		–	–		++++	–
Meningococcic infections	++		–	++		–	++++
Ophthalmic infections							
Bacterial							
Gram positive	++++	++++	–	++++		–	+++
Gram negative	+++		–	–		++++	+++
Viral	++		–	–		–	–
Peritonitis	++++	++	–	++++	++	++++	++++
Pertussis	+++		++++	–	++	++	–
Plague	–		–			++++	++++
Pneumococcic infections	+++	++	+++	++++		–	+++
Primary atypical pneumonia	++++		++++	–		–	–
Psittacosis	++++		++++	–		–	+
Q fever, epidemic	++++		++++	–		–	–
Rat bite fever (*Spirillum minus*)	–		–	++		–	–
Rickettsial infections	++++		++++	–		–	–
Salmonella infections	+		+	–	++	+	–
Shigella infections	–		–	–		+	++++
Staphylococcic infections	++++	++++	–	++++		++	++
Streptococcic infections							
Anaerobic streptococcus	–	++++	–	+++		–	+
β Hemolytic streptococcus	++	++++	++	++++		–	++++
Nonhemolytic streptococcus	++	+++	–	++++		+	++
Syphilis	++	+	+	++++		+	–
Tetanus	–		–	++++		–	–
Tuberculosis	–		–	–		++++	–
Tularemia	++		++	–		++++	–
Typhoid fever	+		++++	–	++	+	–
Urinary tract infections							
Aerobacter aerogenes	++++		++++	–		++++	+++
Esch coli	++++		++++	–		++++	+++
Kb pneumoniae	++++		++++	–		++++	+++
Proteus vulgaris	–		–	–		++++	+++
Ps aeruginosa	–		–	–	++++	++++	+++
Staphylococcus	+		–	++++	–	–	–
Ulcerative colitis	++		++	–		++	++

phenicol There would appear to be little choice between the three agents

For treatment of *gram positive* bacterial infections in general penicillin continues to be the most potent and most useful agent For penicillin resistant organisms both bacitracin and aureomycin have proved effective Aureomycin has the advantage over bacitracin in that it can be given by mouth and there is no risk of nephrotoxicity The sulfonamides are effective in many gram positive infections (hemolytic streptococcic, pneumococcic) but less so than penicillin Aureomycin is more potent against gram positive than gram negative organisms and chloramphenicol is more effective in gram negative than in gram positive infections

Gram negative infections present a difficult problem For gonococcic infections, penicillin is the drug of choice For meningococcic infections, sulfadiazine holds first place Streptomycin is more powerful than aureomycin and chloramphenicol, but the latter two have the advantage that they can be given by mouth For specific infec

tions such as bacillary dysentery the sulfonamides are best, and for typhoid fever the only drug worth considering seriously is chloramphenicol

Herpes simplex of the conjunctivae and cornea has improved following the use of aureomycin, and when herpes are infected with staphylococci the results have been good In *herpes zoster,* recent reports suggest strongly that the course of the disease can be altered favorably by the use of aureomycin

Aureomycin and chloramphenicol have a favorable effect in *lymphogranuloma venereum* When secondary infection plays a part in the lesions, then the sulfonamides, penicillin, or streptomycin may be of aid

The treatment of *meningitis* will depend upon the type of infecting organism Meningococcic meningitis is treated most effectively with sulfonamides (sulfadiazine or sulfamerazine) tuberculous meningitis with streptomycin For all other gram positive bacterial meningitides, penicillin should be used along with sulfonamides For all gram negative infections, streptomycin and the sulfonamides should be employed *Pseudomonas aeruginosa* meningitis may respond to polymyxin B after other agents have failed

Ophthalmic infections present difficult problems due to their etiology Antibiotics are used locally in solutions or in ointments For gram positive infections, penicillin, bacitracin, and aureomycin have all been effective For gram negative bacillary infections, streptomycin, aureomycin, and sulfonamides have been excellent Aureomycin has been used in a variety of infections of suspected virus origin with good results

Peritonitis often presents a complicated problem with mixed infection so that it is not surprising that all antibacterial agents have been used successfully The sulfonamides, penicillin, and streptomycin have been used most widely and aureomycin most recently

The treatment of *pertussis* presents many problems, however, rectal suppositories of chloramphenicol, oral aureomycin and polymyxin, as well as aerosol solutions of streptomycin have all been recommended for pertussis The duration of the disease is said to be shortened

Plague can be treated with a combination of streptomycin and sulfonamides

Pneumococcic infections respond most often following penicillin or sulfonamides It is known now that aureomycin, chloramphenicol, and bacitracin will also bring these infections under control

For primary atypical pneumonia, psittacosis, and all rickettsial infections either aureomycin or chloramphenicol should be used Other agents are ineffective although isolated cases of psittacosis have shown improvement following sulfonamides

The treatment of *rat bite fever* and *Weil s disease* continues to be unsatisfactory Rat bite fever (*Spirillum minus*) infections may be improved with the arsphenamines Too few cases have been treated with antibiotics to give more than a tentative opinion Several patients have improved following penicillin and the same can be said for rat bite fever caused by *Streptobacillus moniliformis*

No effective antibiotic has been developed for the treatment of *Salmonella infections* They are all disappointing although temporary improvement and a suppression of the growth of bacteria have been observed There is so much variation in different strains of Salmonella organisms that no single agent has been very impressive in its action

Shigellae infections, such as bacillary dysentery, usually respond well to the sulfonamides

Staphylococcic infections are treated with penicillin For resistant infections, of which there are an increasing number,

aureomycin and bacitracin have a telling effect

Streptococcic infections respond promptly to either the sulfonamides or penicillin Aureomycin, chloramphenicol, and bacitracin are also said to have a positive action With the exception of the anaerobic streptococcus the results have been favorable in most infections

Penicillin remains the best agent for the treatment of syphilis although it is recognized that the clinical lesions of syphilis may regress following aureomycin or chloramphenicol

Penicillin causes the *tetanus* bacillus to disappear from open lesions It should be used with antitoxin along with surgical treatment when the latter is indicated

Streptomycin is the drug of choice in all cases of *tuberculosis* and in *tularemia* The latter disease also responds to aureomycin and chloramphenicol

For *typhoid fever* the only truly powerful agent is chloramphenicol

Urinary tract infections are usually complicated and their treatment must be planned in accordance with the infecting organism

Ulcerative colitis may be relieved symptomatically by a variety of antibiotics but none of them are curative From the table and the brief discussion a rough guide is given to indicate the drug of choice in the treatment of infections This table may be subject to revision with the passage of time To use it properly presupposes a knowledge of the fundamentals in the use of these drugs and the proper diagnosis

5. General Principles of Infection

GEORGE T. HARRELL

SEVERITY

An infection may occur when a susceptible individual is exposed to a particular etiologic agent at a propitious time Disease of any grade of severity may result, ranging from a mild, asymptomatic case through an abortive one to a severe and fatal infection The severity of any particular infectious disease depends upon three factors (1) the number of invading organisms, (2) the virulence of the organisms, and (3) the resistance of the host The relationship of these factors may be expressed as follows

$$\frac{\textit{Number} \times \textit{Virulence}}{\textit{Resistance}} = \textit{Severity}$$

These factors are in dynamic equilibrium The number of organisms to which the individual is exposed is the most variable of the factors which determine the severity of an infection This factor depends largely on the concentration of the infecting agent in air, food, and water, or in the lesions present in another human being It is possible to minimize this factor by suitable control measures applied to the environment The virulence of organisms is not so readily subject to attenuation Resistance—the ability of an individual to combat an infection—constantly fluctuates in the same individual as the result of exposure to infectious agents and as the result of many nonspecific factors which cannot easily be defined

RECOVERY

Recovery results from the development of specific immunity and from nonspecific factors in resistance Therapy is directed toward reducing the number of infecting organisms, so that a lower level of naturally developing resistance is effective, or toward raising the general resistance or specific immunity of the patient, so that the number and effects of the virulent organisms are neutralized The rise of immunity during recovery can usually be measured in the laboratory, and the knowledge thus obtained may be applied to the control of specific therapy Supportive therapy merely supplements specific therapy, with which it should not be confused

CLINICAL PATTERN

Infecting agents enter a new host through three chief portals (1) the respiratory tract, by inhalation (2) the gastrointestinal and the common portion of the upper respiratory tract by ingestion (3) the skin or mucous membranes by contact Some organisms can enter the body by more than one route, and the clinical pat

tern of the disease and the severity of the infection will be altered by the portal of entry, therapy must be designed with this fact in mind For example, the ulceroglandular form of tularemia, contracted by contact is usually much less severe than the typhoid type, contracted by ingestion of the organism, therapy is simpler and more effective in the ulceroglandular form

Each of the specific fevers follows a pattern which is reasonably constant in its time relationships The invasion of the body by the infectious agent precipitates a struggle which results either in the death of the host or in the control of the infecting organisms and the neutralization of their products The natural history of this struggle is reflected in the clinical course of the disease, which usually follows a pattern distinctive enough to produce the clinical entity

Most infectious diseases have a definite incubation period when invasion dissemination, and multiplication of the organism occur During this period therapy may completely prevent or greatly modify clinical disease After the agent has reached its preferred site of growth, the greater increase in the number of organisms and the consequent elaboration of toxic products lead to progressively severe symptoms until the height of the disease is reached In this stage the hour at which therapy is started is of extreme importance since time is required to mobilize sufficient forces for recovery to begin Therapy begun late in the natural course of the disease may have little demonstrable effect

Because of the multiplicity of factors involved in an infection and the wide variation in them therapy must be individually designed for each patient

GROWTH OF ORGANISMS IN THE BODY

Most specific infections have definite characteristics which alter the effectiveness of therapy Some organisms remain outside the cells of the body throughout the natural course of the disease, and hence are more readily attacked by specific measures the beta hemolytic Streptococcus is an example Other organisms, such as the rickettsias and the filtrable viruses, require some substance found only in living tissue cells for their growth and reproduction The therapeutic attack on these intracellular organisms is complicated by the fact that a chemotherapeutic agent must pass cell membranes not permeable to all substances, to attack the organisms directly, or must so alter the metabolism of the host cell that it becomes an inhospitable environment for the infecting organism

Some organisms may cause a fatal illness while lodging on the skin or mucous membrane, as in the case of diphtheria This disease is caused by diffusion of the soluble exotoxin into the blood stream from the membrane where it is formed The organism has little ability to invade the host, but its virulence is not affected by its relative lack of invasive properties

ETIOLOGIC DIAGNOSIS

Because chemotherapeutic agents and immune bodies possess extremely selective action against infecting organisms the choice of the specific measures used should be based on the demonstration of the etiologic agent Every attempt should be made to obtain an accurate etiologic diagnosis before specific therapy is begun Recovery of the organism, which is the most accurate method of diagnosis may be extremely difficult in previously immunized patients or in those who have had specific therapy administered on suspicion of the disease

Mixed infections or those in which the severity is increased by secondary invasion, usually respond more poorly to therapy than those due to a single organism When the local resistance of the mucous membranes of the respiratory tract is lowered by a rickettsial infection such as Rocky Mountain spotted fever, the bacterial flora of the

mouth may gain a foothold, therapy directed at the rickettsias may not affect the bacteria

LOCALIZED INFECTIONS AND COMPLICATIONS

Special therapeutic measures are necessary when infections have localized—for example, when meningococci circulating in the blood localize on the meninges, or when ulceroglandular tularemia causes pneumonia by spreading to the lungs through the lymphatics and veins These focalized infections are part of the general disease process, as it is seen in some individuals, and should not be considered as complications

Special therapeutic measures are also required in complications which develop as a result of a specific infection Acute glomerulonephritis following scarlet fever, and myocarditis after diphtheria are examples Other complications such as serum sickness and drug fever, are a result of therapy with immune sera or antitoxins, or with specific drugs such as penicillin

Although in most cases the natural process of healing would eventually lead to absorption of the inflammatory exudate of a localized infection or to its spontaneous evacuation as pus, prompt surgical intervention in suitable cases may reduce the number of complications

REINFECTIONS, CROSS INFECTIONS, AND CARRIERS

The therapy of a specific fever is incomplete without the inclusion of measures to protect the family, nurses, and physicians from undue exposure to the etiologic agent Similarly, the patient should be protected from cross infection with another organism carried by a different individual and from reinfection with the same one, especially where a vector or animal reservoir of disease is involved in its transmission

Therapy is incomplete until organisms are completely eradicated from the patient so that a carrier state does not develop Carriers may be found following diphtheria scarlet fever, or typhoid fever, for example An immune individual who has recovered from his clinical disease may harbor virulent organisms asymptomatically in some local area where immunity alone is unable to eradicate them completely Periods of isolation, though often dictated by law, should be governed in addition by bacteriologic studies which can detect the carrier state Often specific chemotherapy or surgical removal of a chronically infected organ, such as the tonsils or gallbladder, may be required to eradicate the organisms

General Principles of Therapy

SUPPORTIVE THERAPY

Rest

Supportive therapy is intended to aid the natural mechanism of recovery from any infection Rest is the first therapeutic measure which an infected individual will usually apply to himself In some unknown fashion rest plays a part in resistance In localized infections immobilization of the part helps prevent the breaking up of the barrier imposed by inflammation and hinders generalized spread

Although an important part of supportive therapy bed rest is not without its dangers Early ambulation following surgical operations has been advocated to reduce the incidence of such complications as hypostatic pneumonia and phlebitis the

same dangers are present in prolonged or debilitating infections The incidence of thrombophlebitis and of urinary stones is higher in patients with any infection who are kept in bed for long periods of time than in those who are permitted to be up early In each individual case the dangers of prolonged bed rest must be weighed against the benefits

Clinically it has been observed that mental rest is an important factor in the recovery from certain specific diseases especially tuberculosis, physical rest alone does not suffice Support of the patient's morale improves his cooperation with therapy and hastens convalescence

Caloric Intake*

Fever increases the metabolic requirements of the body For an average sized man, approximately 140 calories for each degree Fahrenheit of temperature elevation (252 calories for 1 degree centigrade) are necessary above basal requirements to maintain nutrition The increased caloric demand can be met by increasing the dietary intake with almost any food Even children whose metabolism is normally higher than that of adults will not only maintain their weight but may actually gain weight during the illness if supportive therapy is adequate Unless an adequate caloric intake is maintained in severe and prolonged infections pronounced muscular wasting and loss of weight occur as the disease progresses The loss in flesh may be masked by the general interstitial edema which occurs during the acute phase of many diseases but the wasting will become evident during convalescence

In the first few days of most illnesses the patient will take some food and fluid by mouth If the illness is not severe or if specific therapy may be expected to cut short the clinical course, no other measures may be required to maintain nutrition If, on the other hand, the patient becomes delirious, comatose, or uncooperative and the desired intake is not obtained the diet should be supplemented or replaced by liquid feedings with a high protein content

* See also Chapter 51

Many children are unable to take the amount and type of food required, and should receive gavage feedings as soon as they refuse the diet. This procedure tires the patient less than prolonged attempts to feed him a general diet, is simpler than parenteral alimentation, and saves nursing time If necessary, either adults or children can be maintained for days with gavage feedings given every two hours through a large caliber nasal tube left in the duodenum The tube should be washed out with water after each administration of food or medicine It is wise to change the tube from one nostril to the other at least every forty-eight hours the nose and pharynx should be rested several hours before reinsertion

Protein Intake*

The quality of the diet is more important however than the quantity Diet plays a large part in resistance to infection While we do not know exactly what components of the diet are responsible for raising the nonspecific resistance, it is becoming increasingly evident that the protein intake is of great importance in supportive therapy The increased excretion of nitrogen in the urine during acute infection may simply mean that protein is being utilized for fuel and the nitrogen groups discarded On the other hand, infection may increase the need for some specific metabolic grouping and the body may be sacrificing tissue protein to obtain the vital element or group A hint that this latter theory may be correct is found in the fact that the amount of nitrogen excreted by severely burned patients is decreased when methionine is administered

* See also Chapter 51

The *amount of protein required* to maintain nitrogen balance in a patient with a prolonged and severe infection may be very large Experience with Rocky Mountain spotted fever, for instance, has *indicated* that in most cases at least 4 Gm of dietary protein per kg body weight will be required daily to produce a positive nitrogen balance In rare instances as much as 9 Gm per kg has been required It is impractical to attempt to maintain protein balance by the intravenous administration of preformed proteins in plasma albumin, and blood The balance can be more easily maintained by a very high dietary protein intake, which can be achieved with the use of supplementary feedings administered by gavage if necessary In our experience, the use of amino acids or protein hydrolysates either orally or intravenously, has offered no advantage over food

The intake of proteins should be increased as soon as a severe infectious disease is suspected in order to prevent the development of a full blown protein deficiency The amount of protein given should depend on the age of the patient and the clinical severity of the disease, children normally require approximately twice as much protein per kilogram of normal body weight as do adults Because damage to the liver occurs in many moderately severe or severe infections, the diet should also be relatively low in fat and high in carbohydrate Any type of nutritious food in easily digested form is satisfactory

Should supplementary or replacement feedings be necessary, and especially if they are given by gavage, a liquid food is more convenient to use The requirements for protective foods—proteins and vitamins—can be met in this fashion A formula which has proved satisfactory is as follows skimmed milk, 850 cc, powdered milk, 100 Gm, corn syrup 75 Gm, concentrated fish oil to furnish 800 units of vitamin D and 2500 units of vitamin A, niacinamide, 25 mg, ascorbic acid, 0 15 Gm, thiamin chloride, 5 mg, riboflavin 5 mg, menadione 1 mg, or a water soluble synthetic equivalent, 5 mg This amount contains 115 Gm of protein, a negligible amount of fat, 118 Gm of carbohydrate, 932 calories (0 9 per cc), and adequate vitamins If the caloric intake must be increased, substitution of whole milk for the skimmed milk will add 33 Gm of fat the formula will then contain 1238 calories (1 2 per cc) The mixture thickens upon refrigeration and should be warmed to body temperature before administration It has a consistency and flavor similar to malted milk, the addition of chocolate syrup makes it sufficiently palatable to be drunk from a cup

Vitamin Requirements*

It is generally assumed that the requirement for all vitamins is increased in infection but the actual need is as yet unknown The excretion of vitamins in the urine has been found to be increased in many infections, especially in Rocky Mountain spotted fever, the increased excretion reflects the need for increased intake to maintain stores as well as blood levels, and to insure against deficiency states It should be kept in mind that a deficiency of the water soluble vitamins may be precipitated by washing them out of the body through vigorous fluid replacement therapy, as well as by restricting the intake

The incidence and severity of infections are said to be increased when a deficiency exists, and a beneficial effect on the immune response and on the course of various diseases has been observed following the administration of vitamin supplements The administration of vitamins A, C and D, according to some authors appears to increase the resistance of the gastrointestinal tract to tuberculous infection and to promote the healing of lesions already present Vitamins A, B_1 C, and K may be

* See also Chapter 32

given in full therapeutic doses in severe generalized infections because of their possible effect on local infection shock, capillary fragility and bleeding tendency respectively Some members of the B complex are thought to improve the antibody response but this is still in dispute

The metabolism of some vitamins takes place partially in the liver and may be upset in infections which cause liver damage For instance niacin (nicotinic acid) must be methylated before it is used in the presence of liver damage niacinamide should be administered In some instances the disease interferes with the synthesis of prothrombin by the liver even though absorption of vitamin K is unimpaired In other instances the therapy being given decreases the synthesis of the vitamin by bacteria in the bowel The prolonged administration of sulfonamides for instance may alter the bacterial flora and hence interfere with the production of the vitamin from food The absorption of orally administered menadione is not affected however The rapidity with which oral lesions resembling B complex deficiencies follow the administration of aureomycin and other antibiotics suggests the further possibility that the utilization of the vitamins by enzyme systems of cells may actually be antagonized

When vitamin supplements are given in large quantities it is probably wise to administer all the recognized vitamins in proper ratio and to use those derived from natural sources in order to insure the inclusion of substances as yet unidentified which are present only in traces The doses given should be three to four times as great as those required to maintain health under normal conditions This amount is undoubtedly excessive but exact information on vitamin requirements is not available The oral route of administration is usually satisfactory

Maintenance of Fluid Balance*

The disturbance in water balance caused by fever may lead to dehydration Fluid is lost in perspiration and is expired through the lungs as respirations increase with fever Dehydration of tissue lessens the transport of soluble metabolites across cell membranes Loss of the fluid component of blood increases the tendency toward circulatory failure and thrombosis The lack of fluid available for excretion through the kidneys contributes to the development of prerenal azotemia and to disturbances in mineral balance The fatal course of cholera for instance is due, not to systemic intoxication from the infecting organism but to dehydration caused by the increased permeability of the intestinal mucosa the hypermotility of the bowel prevents reabsorption of the fluid thus lost

It is essential that fluid balance be maintained but care must be exercised in deciding on the amount of fluid given and on the route of administration It is possible to overload the circulation in comatose patients by unwisely chosen fluid therapy administered in excessive quantities through an indwelling duodenal tube as well as parenterally Patients who are dehydrated at the time they are first seen especially those who have elevated blood levels of nonprotein nitrogen or low blood chloride levels should be given calculated amounts of an isotonic solution of sodium chloride until the urinary flow returns to normal Those patients who have nitrogen retention but normal blood chlorides should be given a 5 per cent solution of dextrose in water

The administration of glucose and saline will cause the blood chemical values for nonprotein nitrogen and chloride to return to normal but in the presence of altered capillary permeability plasma may be washed out of the vascular tree presumably into the interstitial tissue space The circulating plasma protein may thus be reduced

* See also Chapter 19

sufficiently to alter osmotic equilibrium further and to allow more crystalloids to remain outside the blood vessels This vicious cycle leads to peripheral circulatory collapse (medical shock) The serum proteins drop precipitously in such instances the circulating blood volume is decreased, and the extravascular fluid space increased

The type and quantity of parenteral therapy given should be governed by clinical judgment and by careful laboratory control No single injection should contain more than 20 cc of fluid per kg body weight If fluids can be taken orally, the same effect can be achieved with less danger of precipitating pulmonary edema The efficacy of supportive treatment should be checked by repeated laboratory determinations to be certain that the desired results are being obtained In severely ill patients for instance it may be desirable to determine the total serum proteins at intervals of three to eight hours during the critical period of the disease

Maintenance of Acid Base Balance*

By causing an increase in the combustion of carbohydrates and body fat an infection may upset the acid base balance of the body organic acids are produced in greater quantities and more base is needed for their neutralization Sodium is excreted in an attempt to neutralize the organic acids produced thus the amount of the available base is decreased and the carbon dioxide combining power may be reduced Sixth molar sodium lactate solution should then be administered either intravenously or subcutaneously In children any infection may induce nausea vomiting or diarrhea with loss of fluid and base hence a low carbon dioxide combining power is seen more frequently in children than in adults

Since calcium is excreted along with the sodium both ions should be supplied by replacement therapy designed to replenish fluid loss and correct the acid base balance otherwise the calcium ion will be depressed and tetanic cramps may be produced The temporary alkalosis induced by hyperventilation such as may occur in pneumonia may reduce the ionization of calcium and help to bring out a latent Trousseau sign when a blood pressure cuff is applied

Many infections are said to induce anatomic changes in the adrenal cortex Damage to both adrenal cortices by tuberculosis reduces the amount of circulating hormone which is necessary for the reabsorption of sodium by the kidney tubules Sodium is lost from the blood, potassium is called out of cells to maintain ionic equilibrium and the level of potassium in the blood rises to the point of producing symptoms of intoxication Replacement of water, sodium and chloride is usually sufficient to restore equilibrium, unless the cortices are totally destroyed as in the Waterhouse Friderichsen syndrome Then it may be necessary to administer aqueous adrenal cortical hormone simultaneously Desoxycorticosterone and cortisone also are helpful

The greater part of the potassium in the body is normally found intracellularly if cellular destruction by the infectious process is great increased quantities of potassium may be liberated into the blood This ion is usually excreted quickly by the kidneys if adequate sodium is present, hence, a deficiency in total body potassium may exist during recovery from a hyperacute or prolonged infection especially if dehydration has been severe and has been actively combatted Such a deficiency is difficult to detect from the level of potassium in the circulating blood Convalescence may be delayed however, until the deficiency is made up

In addition to the loss of basic ions a loss of chlorides occurs during the sweating which accompanies fever The administration of antipyretics increases sweating The muscular twitching and muscular or intes

* See also Chapter 19

tinal cramps which result from a chloride deficiency can be reduced by the oral administration of salt tablets Unless these are enteric coated however nausea may result from gastric irritation Bouillon cubes dissolved in water furnish 2 to 3 Gm of salt in a palatable broth and are a convenient source of both sodium and chloride ions and of fluid

Measures to Decrease the Permeability of Membranes

The extravascular fluid available for dilution of thiocyanate is increased during the acute phase of some infections In some diseases such as pneumococcal pneumonia the defect in capillary permeability is small so that only the tiniest molecules—water crystalloids and ions—are lost from the circulation In other diseases such as Rocky Mountain spotted fever the defect is greater in degree and larger molecules—albumin or even red blood cells—are apparently lost from the circulation The increase in extravascular fluids is often accompanied by visible edema and reaches its maximum at about the clinical peak of the disease During recovery the fluid stored outside the vascular tree is reabsorbed and excreted in the urine the diuresis which begins in convalescence has been recognized for years The mobilization of fluid and loss of edema may take as long as a week

When the quantity of fluid confined within blood vessels and within the extravascular spaces is compared with the changes in weight of the individual a disproportion is frequently found The comparison suggests that the permeability of cells outside the vascular tree may also be altered so that fluid accumulates within the body cells as well as in the interstitial spaces This excessive hydration of cells may affect the function of organs in which vascular lesions are not pronounced Clinical evidence that nerve cells are hydrated excessively is found in the stupor, tremor and medullary respiratory arrest occasionally seen in fatal acute infections such as Rocky Mountain spotted fever and meningitis Since these infections are not caused by a neurotropic virus it is evident that specific parasitization of nerve cells is not necessary for this change to occur

The mechanism responsible for altering the permeability of membranes at the peak of the disease is obscure The maximum changes in capillary permeability occur at the time when immunity should be rising rapidly and beginning to attain ascendency over the infection The edema in Rocky Mountain spotted fever for instance usually appears at the end of the second week (the time required for the development of antibodies) and the subsequent clinical improvement would suggest that the immune balance is being tilted The neutralization of antigen by antibodies—either circulating or fixed to tissue cells—must produce a substance which directly affects membranes It has been known for years that antigen antibody reactions liberate a histamine like substance That histamine and similar substances alter capillary permeability is readily demonstrated by the production of a wheal when histamine is injected into the skin Observations in acute infections suggest that an antigen antibody effect involves the general circulation and alters the permeability of the entire vascular tree and possibly of tissue cells as well

In view of the possibility that the increase in permeability of membranes is at least partially due to the effects of an antigen antibody reaction the administration of antihistaminic agents during the first and second weeks of rash in certain severe infections may be helpful in reducing the disturbances in fluid distribution

Support of the Circulation

Recurrent chills with constriction of the peripheral vessels may prove exhausting to a debilitated patient During the initial

phase of the chill, the intravenous administration of ionized calcium may interrupt it or lessen its severity. Deep sedation or the application of external heat may abolish the shivering. The patient usually attempts to warm himself by using extra blankets, a hot bath, an electric blanket, or warm water bottles are more effective.

Central (myocardial) circulatory failure resulting from infection should be treated in the same fashion as myocardial failure from any other cause.* So far as possible myocardial damage should be prevented by the prompt administration of suitable specific antibodies, such as the antitoxin of diphtheria, or by prophylactic chemotherapy—for instance, the prompt administration of sulfonamides or penicillin when streptococcal infections develop in persons with pre-existing rheumatic heart disease. If decompensation is imminent or has actually occurred, the active principles of digitalis should be given. A myocardium damaged by infection is likely to be more sensitive to digitalis than one damaged by a mechanical disturbance; the drug may have to be given in small doses when infection is present, and may not be as effective.

The circulating blood volume has been found to be increased in some diseases, such as pneumococcus pneumonia. In such cases the administration of excessive amounts of fluid, especially by vein, may produce dilatation of the right side of the heart. This danger is increased if the myocardium has been previously damaged by other diseases or has been affected by the current infectious process. Though the prophylactic administration of digitalis will not protect an undamaged heart muscle from the harmful effects of fluid therapy, the therapeutic use of the drug is rational in cases where failure has been precipitated by excessive fluids or by injury to the myocardium.

As the defect in capillary permeability is repaired with recovery, it is conceivable that the increase in blood volume which accompanies reabsorption of stored extravascular fluids may be sufficient to produce frank failure when the heart is already on the border of decompensation.

Peripheral circulatory failure is more difficult to recognize and probably occurs more frequently than central circulatory failure. It is likely that peripheral collapse is a common cause of death in acute infections. It has been found that the blood volume is reduced during the acute phase of Rocky Mountain spotted fever and returns to normal during the period of vascular repair in recovery. The decrease in blood volume usually occurs simultaneously with a drop in serum proteins, and reflects the reduced amount of water held by osmotic attraction in the vascular tree.

Peripheral collapse due to infection—"medical shock"—should be treated in the same fashion as peripheral collapse due to trauma—"surgical shock." The circulation should be supported by the administration of whole blood, plasma, or serum albumin. All these agents accomplish the same purpose—that of increasing the intravascular osmotic attraction, so that more fluids are retained in the vascular bed and the circulating blood volume is raised. Administration of these substances is not designed to increase the antibody titer of the blood. The quantity given in any single injection should not be too great. Since the myocardium is more frequently damaged by infection than by trauma, the danger of precipitating central circulatory failure is greater in "medical shock" than in "surgical shock."*

Prevention of Anoxia

Anoxia may arise when inflammation of the pulmonary alveoli interferes with diffusion of oxygen, or when oxygen transport by the circulation is inefficient. Because of the depressing effect of powerful hypnotics

* See also Chapter 10

* See also Chapter 43

on respiration the possibility of inducing anoxia by this means must be kept in mind respiratory stimulants may have to be given simultaneously when hypnotics are necessary

If a suspicion of anoxia arises oxygen should be administered a continued deficiency in available tissue oxygen leads to an irreversible alteration of local enzyme systems Oxygen therapy should be given by a nasal tube facial mask or oxygen tent as soon as impending circulatory failure pneumonia or myocardial failure is suspected If the administration of oxygen is withheld until cyanosis is deep and the indications are obvious irreparable damage may have been done *

Measures to Decrease Metabolism

The thermostatic control of the body is upset by the toxic effect of the infection on the medulla and on the peripheral capillary bed Rest reduces the metabolic requirements if the requirements are not adequately controlled by simple rest in bed sedation should be used

Antipyretic drugs decrease metabolism by lowering the temperature Since these drugs usually cause increased sweating the chloride intake must be more carefully observed when they are given in large quantities Mechanical means of dissipating heat —cold enemas sponges packs and baths— will reduce the temperature The sudden local chilling however may possibly lower resistance to another infection such as pneumonia and may also induce circulatory changes

Symptomatic Therapy

Most generalized infections are accompanied by headache and muscular aching Simple analgesics such as aspirin are often all that is necessary to effect relief When severe headache extreme restlessness or increasing drowsiness is due to elevation of the spinal fluid pressure because of gen[eralized] edema or localization of the in[fec]tion reduction of the pressure halfway [to] the normal level may result in rapid sym[p]tomatic improvement

In infections where organisms settle in the filter bed of the lungs cough may [be] an annoying or even exhausting sympt[om] Suppression of cough by sedatives may [pro]duce anoxia often especially in dehydra[ted] patients inhalations of steam containin[g] soothing volatile substance such as ment[hol] or benzoin are more effective since t[hey] also loosen accumulations of inspissa[ted] mucus

Abdominal distention with gas may [in]terfere with food intake and fluid thera[py] Reduction in the carbohydrate content [of] the diet and the use of neostigmine [or] other drugs to stimulate peristalsis will h[elp] to overcome the paralytic ileus and to [re]duce any respiratory embarrassment [Dis]tention may also be relieved by const[ant] gastrointestinal suction but if this meas[ure] is employed particular attention should [be] paid to fluid and mineral replacem[ent] therapy

When diarrhea is a symptom of [the] disease or has resulted from gavage fe[ed]ings fluids and electrolytes—particula[rly] chloride and base—may be lost in la[rge] quantities a similar loss may result fr[om] vomiting Antispasmodics (given paren[te]rally at first) adsorbents such as kaolin [or] constipating substances such as calcium [car]bonate or aluminum hydroxide may h[elp] to control the diarrhea

The toxemic symptoms resulting fr[om] infection often can be dramatically relie[ved] or completely suppressed by ACTH or c[or]tisone In some instances however the [use] of these hormones seems actually to p[ro]mote spread of the infection Whet[her] simultaneous administration of spec[ific] chemotherapy may permit their safe use [as] supportive therapy will depend on furth[er] experience

* See also Chapter 41

Prevention and Treatment of Bacterial Complications

In many severe or prolonged infections death results from secondary bacterial invasion of the body occurring in the course of the debilitating illness The lungs are especially vulnerable though the skin and deep veins of the legs and abdomen are also frequently affected Maintenance of nutrition and support of the circulation will help to prevent such complications

In those diseases which are accompanied by edema pulmonary congestion commonly occurs as the result of generalized interstitial edema Protein containing edema fluid *in the lungs furnishes an excellent culture* medium for bacteria ordinarily found in the mouth and may lead to pneumonia The full development of pneumonitis can sometimes be prevented by the administration *of preformed proteins to control the* edema and by frequent turning of the patient If the edema is cardiac in origin the heart failure must be treated

Since penicillin is a relatively harmless drug it is probably wise to begin the immediate parenteral administration of an aqueous solution of penicillin G (25 000–50 000 units every two to three hours) when patients exhibit the slightest signs of pulmonary disease developing in the course of a generalized infection A similar dose will prevent bacterial infection of the skin such as may occur in the lesions of smallpox

If secondary bacterial infection develops during the course of a generalized infection which is being treated with penicillin or aureomycin (drugs which are effective against most gram positive cocci) or if the *secondary infection does not respond* to these drugs it is most likely due to a gram negative rod and should be treated with streptomycin sulfadiazine chloramphenicol *or a combination of these agents* *

* See also Chapter 4

Nursing Care

In most uncomplicated infections the maintenance of nutrition and good nursing care are the most important factors in supportive therapy Diet and feeding have been discussed in preceding sections

Nursing care is directed at the prevention of complications If the patient is not able to take oral feedings or is comatose the danger of parotitis should be combatted by swabbing the gums several times daily with the juice of half a lemon in an ounce of glycerin or mineral oil Pneumonia is a very serious complication in many infectious diseases and is the one which most *frequently leads to death especially in older* individuals Frequent turning of the patient will delay the development of hypostatic pneumonia by increasing aeration of the lungs

Necrosis of the skin may occur over the pressure points in comatose patients or may develop in areas of severe rash especially if there has been hemorrhage Because of the maceration of the skin produced by sweating furuncles may start in the pores or hair follicles Meticulous constant gentle, and painstaking care must be given to the skin to prevent breaks through which secondary bacterial invaders can enter or the development of decubitus ulcers Frequent turning of the patient and the use *of a rubber ring will help prevent the latter* complication

The development of thrombophlebitis which so commonly accompanies prolonged *infections* can be *delayed or prevented by* graduated exercises performed in bed During the acute phases of the disease the exercise must be passively performed with help from the nurse as convalescence *becomes* established active exercise can be begun by movement of the feet and legs in bed The amount of exercise can be gradually increased as the patient regains *his strength* The use of anticoagulant therapy in pre

venting the extension of thrombophlebitis is discussed in Chapters 11 to 13

The nurse should serve as a buffer between the patient and his family, well meaning visitors and friends who are likely to exhaust him physically and emotionally

Summary

All supportive measures are designed to tide the patient over the acute phase of his infection, to alleviate symptoms and to allow time for immunity to develop They should not be neglected in cases where the natural course of the disease is interrupted by specific therapy To be effective the therapy of infectious diseases must be based on a consideration of the etiologic agent the natural mechanism of recovery by the development of immunity in the host and the pathologic immunologic and physiologic response of the host to the infectious agent

SPECIFIC THERAPY

Chemotherapy*

Relation to Immunity Chemotherapy is aimed at sterilization of the infectious process but this goal rarely is achieved Usually the etiologic agent is only inhibited in its growth and reproduction recovery must still be brought about by the immune mechanism of the body When the number of invading organisms is kept to a minimum by chemotherapeutic agents a lower level of resistance in the host is effective in preventing spread of the infection and in promoting recovery The spectacular response to chemotherapy often obtained in reinfections or in infections occurring in immunized individuals is explained by this mechanism If the virulence as well as the number of organisms could be reduced a still lower level of resistance would be effective and clinical recovery would begin even earlier

* See also Chapter 4

Chemotherapy may injure an infectious agent sufficiently to alter its invasiveness or reduce its ability to produce harmful substances under sulfonamide therapy, for instance, capsules frequently disappear from pneumococci No clear evidence has been presented that chemotherapy inactivates secretions of bacteria after they are formed or detoxifies harmful substances bound within the cell as endotoxins Since chemotherapeutic agents do not directly raise the resistance of the host the use of antisera and antitoxins when they are available to increase circulating antibodies rapidly should not be neglected

Chemotherapy will be most effective early in the course of acute infections when the organisms are continually bathed by blood serum interstitial fluid, or other fluids containing the drug The high concentration of the drug in the urine, for instance reduces the number of organisms available for reinfection of the crypts on the surface of the urinary tract Because of its limited therapeutic spectrum an antibiotic may eradicate one organism in a mixed infection only to allow the multiplication of another which has been suppressed by the first organism As a general rule chemotherapy is more effective in acute infections than in chronic ones and more effective against those due to a single susceptible organism than against those caused by mixed flora

Combinations of Drugs The possible potentiation of one chemotherapeutic agent by another suggests the use of combined therapy in severe infections It is known that the antibiotics do not attack the same enzyme systems of bacteria as do the sulfonamides since their action is not blocked by *p*-aminobenzoic acid (PABA) one of the B complex vitamins Since the therapeutic spectra of chemotherapeutic agents overlap to some extent a combination of two or more antibiotics or the simultaneous ad

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In many severe or prolonged infections death results from secondary bacterial invasion of the body occurring in the course of the debilitating illness The lungs are especially vulnerable though the skin and deep veins of the legs and abdomen are also frequently affected Maintenance of nutrition and support of the circulation will help to prevent such complications

In those diseases which are accompanied by edema pulmonary congestion commonly occurs as the result of generalized interstitial edema Protein containing edema fluid *in the lungs furnishes an excellent culture* medium for bacteria ordinarily found in the mouth and may lead to pneumonia The full development of pneumonitis can sometimes be prevented by the administration of preformed proteins to control the edema and by *frequent turning of the patient* If the edema is cardiac in origin the heart failure must be treated

Since penicillin is a relatively harmless drug it is probably wise to begin the immediate parenteral administration of an aqueous solution of penicillin G (25 000–50 000 units every two to three hours) when patients exhibit the slightest signs of pulmonary disease developing in the course of a generalized infection A similar dose will prevent bacterial infection of the skin such *as may occur in* the lesions of smallpox

If secondary bacterial infection develops during the course of a generalized infection which is being treated with penicillin or aureomycin (drugs which are effective against most gram positive cocci) or if the secondary infection does not respond to these drugs it is most likely due to a gram negative rod and should be treated with streptomycin sulfadiazine chloramphenicol or a combination of these agents *

* See also Chapter 4

Nursing Care

In most uncomplicated infections the maintenance of nutrition and good nursing care are the most important factors in supportive therapy Diet and feeding have been discussed in preceding sections

Nursing care is directed at the *prevention* of complications If the patient is not able to take oral feedings or is comatose the danger of parotitis should be combatted by swabbing the gums several times daily with the juice of half a lemon in an ounce of glycerin or mineral oil Pneumonia is a very serious complication in many infectious diseases and is the one which most *frequently leads to death especially* in older individuals Frequent turning of the patient will delay the development of hypostatic pneumonia by increasing aeration of the lungs

Necrosis of the skin may occur over the pressure points in comatose patients or may develop in areas of severe rash especially if there has been hemorrhage Because of the maceration of the skin produced by sweating furuncles may start in the pores or hair follicles Meticulous constant gentle and painstaking care must be given to the skin to prevent breaks through which secondary bacterial invaders can enter or the development of decubitus ulcers Frequent turning of the patient and the use of a rubber ring will help prevent the latter complication

The development of thrombophlebitis which so commonly accompanies prolonged infections can be delayed or prevented by graduated exercises performed in bed During the acute phases of the disease the exercise must be passively performed with help from the nurse as convalescence becomes established active exercise can be begun by movement of the feet and legs in bed The amount of exercise can be gradually increased as the patient regains his strength The use of anticoagulant therapy in pre

venting the extension of thrombophlebitis is discussed in Chapters 11 to 13

The nurse should serve as a buffer between the patient and his family well meaning visitors and friends who are likely to exhaust him physically and emotionally

Summary

All supportive measures are designed to tide the patient over the acute phase of his infection to alleviate symptoms and to allow time for immunity to develop They should not be neglected in cases where the natural course of the disease is interrupted by specific therapy To be effective the therapy of infectious diseases must be based on a consideration of the etiologic agent the natural mechanism of recovery by the development of immunity in the host and the pathologic immunologic and physiologic response of the host to the infectious agent

SPECIFIC THERAPY

Chemotherapy*

Relation to Immunity Chemotherapy is aimed at sterilization of the infectious process but this goal rarely is achieved Usually the etiologic agent is only inhibited in its growth and reproduction recovery must still be brought about by the immune mechanism of the body When the number of invading organisms is kept to a minimum by chemotherapeutic agents a lower level of resistance in the host is effective in preventing spread of the infection and in promoting recovery The spectacular response to chemotherapy often obtained in reinfections or in infections occurring in immunized individuals is explained by this mechanism If the virulence as well as the number of organisms could be reduced a still lower level of resistance would be effective and clinical recovery would begin even earlier

Chemotherapy may injure an infectious agent sufficiently to alter its invasiveness or reduce its ability to produce harmful substances under sulfonamide therapy for instance capsules frequently disappear from pneumococci No clear evidence has been presented that chemotherapy inactivates secretions of bacteria after they are formed or detoxifies harmful substances bound within the cell as endotoxins Since chemotherapeutic agents do not directly raise the resistance of the host the use of antisera and antitoxins when they are available to increase circulating antibodies rapidly should not be neglected

Chemotherapy will be most effective early in the course of acute infections when the organisms are continually bathed by blood serum interstitial fluid or other fluids containing the drug The high concentration of the drug in the urine for instance reduces the number of organisms available for reinfection of the crypts on the surface of the urinary tract Because of its limited therapeutic spectrum an antibiotic may eradicate one organism in a mixed infection only to allow the multiplication of another which has been suppressed by the first organism As a general rule chemotherapy is more effective in acute infections than in chronic ones and more effective against those due to a single susceptible organism than against those caused by mixed flora

Combinations of Drugs The possible potentiation of one chemotherapeutic agent by another suggests the use of combined therapy in severe infections It is known that the antibiotics do not attack the same enzyme systems of bacteria as do the sulfonamides since their action is not blocked by *p* aminobenzoic acid (PABA) one of the B complex vitamins Since the therapeutic spectra of chemotherapeutic agents overlap to some extent a combination of two or more antibiotics or the simultaneous ad

* See also Chapter 4

ministration of a sulfonamide and an antibiotic, may be useful in attacking extremely severe infections through several vulnerable points in the infecting organism

The principle of competition between substances for a place in an enzyme system should be considered in designing chemotherapy For instance, all sulfonamides are definitely contraindicated throughout the course of rickettsial diseases since their administration to human beings as well as to experimental animals has increased the severity of the illness Discovery of the harmful effects of the sulfonamides led to the clinical trial of PABA which is antagonistic to the sulfonamides in the test tube The drug apparently inactivates an enzyme necessary for growth of the rickettsias and accelerates cell metabolism of the body by increasing respiration As a result the rickettsias suffer in the competition with the host cells and the multiplication of the organism is thought to be hindered

Since aureomycin is not inactivated by PABA and apparently has the property of penetrating cell membranes and attacking rickettsias within cells it may prove that a combination of aureomycin (or chloramphenicol) with PABA will be even more effective in the therapy of rickettsial diseases than either drug alone

By effecting a more rapid eradication of the infecting organism combined therapy would also reduce the possibility of the development of drug fastness However, a combination of antibiotics may not always achieve potentiation of chemotherapeutic effect If chloramphenicol is given before or simultaneously with penicillin for instance, the bactericidal action of penicillin is antagonized If a staphylococcus has become drug fast to aureomycin the addition or substitution of terramycin will not overcome the resistance to therapy apparently the two antibiotics attack the organism at the same point

Toxic Effects*

The possible harmful effects of a specific chemotherapeutic agent must be considered in the selection of a drug Toxic reactions may appear with the first dose of a drug (idiosyncrasy), in such cases subsequent use of the same agent or a closely related drug will usually produce an identical effect Other toxic symptoms do not appear until the patient has been receiving the drug for several days as in the effect of streptomycin on the eighth nerve The damage follows large doses of the drug and is irreversible Other reactions are allergic in character and may take the form of a local skin eruption or a sudden fever

Immune Therapy†

The natural course of an infection may be altered by specific measures which increase the immunity of the host more rapidly than does the natural mechanism of recovery As immunity develops both cellular and humoral antibodies are formed Stimulation by live virulent organisms produces antibodies to all the antigens contained or secreted by the organism

Immune therapy may be active (injection of antigens to stimulate the formation of immune bodies) or passive (injection of preformed immune bodies obtained from another individual)

As a general rule if no definite response is observed after adequate doses of a proven potent serum have been administered for three days by a route which will reach the organisms further immune therapy is not likely to be effective

Complement Since many antigen antibody reactions are dependent upon the presence of fresh complement it is occasionally advisable to give transfusions of fresh blood simultaneously with the administration of immune serum The spinal fluid normally contains no complement in men

* See also Chapter 4
† See also Chapter 3

ingococcus meningitis the intrathecal injection of several cubic centimeters of fresh human serum from a healthy donor will occasionally mean the difference between the success and failure of intrathecal immune therapy In many cases phagocytosis of organisms in pus does not occur until the injection of antiserum is followed by the administration of complement

Reactions to Serum Therapy Since most immune sera are prepared in animals the danger of hypersensitivity reactions should be kept in mind Before an immune serum is injected in therapeutic doses the patient should be given intradermal or conjunctival tests with serum from the species of animal in which it is prepared If a reaction to the test dose occurs, desensitization of the patient to serum from the donor species of animal will usually allow the safe administration of immune therapy

Even in the absence of specific hypersensitivity, dangerous systemic and local antigen antibody reactions may follow the therapeutic administration of antisera

Relation to Chemotherapy Antisera for passive immune therapy are becoming less widely available since the introduction of potent chemotherapeutic agents Antitoxins are still available though the need for them has been reduced by the development of effective vaccines (toxoids) The development of potent chemotherapeutic agents may relegate serum therapy to use only in extremely toxemic patients or in those who have an idiosyncrasy to chemotherapeutic [illegible]

viral diseases no effective chemotherapeutic agent has yet been developed and immune therapy offers the only hope for decreasing the severity of the infection or shortening the period of illness Immune globulin derived from the placenta or from plasma contains a mixture of antibodies effective against several filtrable viruses which are, at present, not susceptible to chemotherapy Since the viruses grow intracellularly, the immune bodies must be administered soon after exposure or early in the incubation period to be most effective, they are less efficacious after clinical disease has become evident

Other Biologic Therapy

Bacteriophage Certain organisms responsible for an infection may be attacked directly by a specific biologic method which does not alter the immunity of the host, as does immune therapy A bacteriophage may be prepared which will effectively lyse the particular organism against which it is lethal, and achieve the same result as would be expected from chemotherapy The material must usually be applied directly to the site where the bacteria are growing

Nonspecific Measures Nonspecific protein shock therapy may be administered by the intramuscular injection of sterile milk protein or the intravenous injection of typhoid flagellar antigen This measure is designed to shake up the immune mechanism, its effectiveness probably depends on the anamnestic reaction, by which many antibodies which once were formed in response to infection or to prophylactic immunization are increased in titer as the result of stimulation by a different antigen

In addition to increasing the immune response, foreign protein therapy elevates the body temperature Artificial fever, whether induced by protein shock or by physical means such as radiant heat or induction with short electromagnetic waves may also act nonspecifically by dilating the arterioles and allowing more effective penetration of immune bodies and *chemotherapeutic* agents into an infected area or by altering capillary permeability and *permitting* these substances to leave the vascular tree Occasionally sufficient fever can be induced to approach or exceed the thermal death point of the infecting organism, so

that it may be killed or at least attenuated and made more susceptible to eradication by the immune processes The induction of artificial fever is not without danger, however, especially in persons with a history of heat exhaustion or heat stroke *

Desensitization The course of a chronic infection may be altered by desensitizing the patient to the organism involved The purpose of this technique is to reduce the cellular reaction which results from the liberation of antigen into a hypersensitive area and hence to lessen the severity of the symptoms In some cases of brucellosis desensitization therapy starting with very high dilutions of antigen may produce a favorable clinical response without demonstrable alteration in immune body titers as determined by agglutination tests

The destruction of infecting organisms by chemotherapy may result in the liberation of increased amounts of antigen into a hypersensitive area The temporary increase in symptoms and the febrile response observed in some patients with chronic brucellosis adequately treated with antibiotics may be due to this mechanism Similarly the occasional occurrence of fever and eosinophilia in leprous patients following the administration of streptomycin may possibly be explained in the same manner Preliminary desensitization with filtrates or vaccines to reduce the local tissue response may be necessary in extremely hypersensitive individuals before chemotherapy can be safely used

Too vigorous attempts at desensitization may do harm the dose of antigens should be suitably adjusted by dilution to avoid febrile or shock reactions Patients with brucellosis often become clinically and immunologically worse after they are given shock doses of desensitizing material either intentionally or following accidental intravenous inoculation

Breakdown of Granulomas The reaction of the body to many infectious agents results in the formation of granulomas. This type of tissue response is more frequently seen in the chronic, long standing infections such as brucellosis, tuberculosis, and syphilis, it may impose a barrier to the free circulation of antibodies so that a high degree of humoral immunity is relatively ineffective Iodides administered by any route effectively dissolve many chronic infectious granulomas The beneficial effect of iodide therapy in mycotic infections illustrates this principle The liberation of increased amounts of antigen following the breakdown of granulomas may be harmful however The administration of iodides to patients with tuberculosis has been known to cause a low grade fever to change abruptly into a high swinging one with an increase in the toxemia of the patient

The development of new chemotherapeutic agents, especially the antibiotics makes the application of the principle of therapy discussed above increasingly important In granuloma inguinale streptomycin and aureomycin apparently penetrate the lesions and healing follows without the use of iodides When planning therapy in other chronic infections it may be wise if time permits and suitable biologic materials are available first to desensitize the patient and then to attain an effective level of the chemotherapeutic agent in the blood and tissues before the infectious granuloma is broken down by iodides

Inhibition of the Antigen Antibody Reaction The occasional harmful effects of antigen antibody reactions may be reduced by inhibiting the reaction or by counteracting the effect of the histamine like substance released Salicylates will inhibit precipitin reactions in vitro this inhibitory effect partially explains the usefulness of salicylates in the control of the acute symptoms of serum sickness By protecting cells from the effect of the histamine like sub

* See also Chapter 45

sions may add to the depressing effect of the poison For this reason also the dose of sedative drugs should be kept at a minimum

During the course of a convulsive disorder, if the respirations become inadequate to maintain life artificial respiration should be administered in a gentle manner

Regional Anesthesia

THE injection technics of the anesthesiologist are becoming increasingly useful in diagnosis and treatment Injections of local anesthetic drugs serve to block nerve impulses If the desired change occurs after the injection it is an indication that the disturbance probably has a neurogenic background Otherwise there is probably an organic change in the involved tissues Used as a method of therapy the injection of local anesthetic drugs improves abnormal neurogenic conditions or those caused by local tissue disturbances Local anesthetic drugs may be injected into the spinal canal where they affect the spinal nerve roots into or around large peripheral nerve trunks or they may be injected to interrupt the impulses of the small nerve filaments in the various tissues

LOCAL ANESTHETIC DRUGS

Injection procedures are usually performed with aqueous solutions of the common drugs such as procaine metycaine intracaine xylocaine pontocaine and nupercaine These drugs may also be used in oil solutions Among other drugs used in therapy are eucupin ammonium sulfate (sarapin) and alcohol These drugs are listed in the order of increasing duration of action Oil solutions and procaine in propylene glycol (efocaine) have a greater duration of action than aqueous solutions but their use is restricted to deep injections Of the local anesthetic drugs procaine is the least toxic the maximum dose of procaine is 1 Gm In equal doses pontocaine is ten times as toxic as procaine and nupercaine is twenty times as toxic as procaine The dosage of these drugs should be appropriately reduced Procaine is used in solutions of 0 5 or 2 per cent Pontocaine is used in a 0 1 per cent solution Nupercaine is used in a solution of 1 1500 or 1 2000 The more concentrated solutions of local anesthetic drugs may be used for nerve blocks for widespread infiltration the dilute solutions should be used

Hyaluronidase may be added to the local anesthetic solution Its effect is to increase the spreading of the solution and thereby to increase the proportion of successful injections

Toxicity

The toxicity of local anesthetics depends in part on the concentration used and in part on total dosage The greater the amount and the more concentrated the solution the more frequent is the incidence of toxic reactions True allergy to local anesthetic drugs rarely occurs Most local anesthetic reactions are caused by a rapid entry of the drug into the blood stream with a resulting high blood concentration and precautions should be taken to prevent this During infiltration protection against intravenous injection is provided by continually moving the needle the injection should be performed during the insertion and withdrawal of the needle When the injection is performed with the needle in one place as for nerve block the plunger

intestinal tract. The possibility that bacteria may develop drug fastness or resistance to subsequent chemotherapy with the same drug must be kept in mind. Furthermore, the alteration in the normal intestinal flora may result in large, loose stools or may interfere with the synthesis of vitamins in the bowel lumen.

stances which are released, the new antihistaminic drugs may reduce the symptoms caused by antigen antibody reactions occurring in the natural course of the disease or by hypersensitivity reactions resulting from specific therapeutic measures

Antihistaminic drugs are more likely to be effective in diseases where the immune balance is rapidly being shifted than in diseases which run a longer course with a more gradual rise in resistance The drugs will probably be more effective in diseases where immunity is largely humoral than in those in which resistance is largely cellular

PROPHYLAXIS

Active Immunization*

Immunization is intended to raise an individual's level of immunity so that he may be exposed to larger numbers of organisms than would otherwise be possible without acquiring active or clinical disease If the exposure can be anticipated in time for the individual to manufacture his own antibodies he may be actively immunized In a few diseases such as rabies the incubation period is long enough for prophylactic immunization to be effective after exposure

Passive Immunization*

In most instances the interval of time elapsing between exposure and the development of clinical disease is too short to permit active immunization In such cases passive immunity may be conferred by the injection of antibodies preformed in another individual or in an animal Passive immunity may also be conferred in some diseases such as measles for which no prophylactic immunizing antigen is yet available

Preventive Chemotherapy

Chemotherapy may be used to prevent as well as to treat infections The differences in the invasiveness of bacteria and in their susceptibility to chemotherapeutic agents must be considered in planning prophylactic measures Sulfonamides will quickly eradicate the highly susceptible meningococcus from the nasopharynx, streptococci will be cleared more slowly, but the implantation of additional organisms will be hindered Pneumococci, on the other hand, are invasive only if local resistance is lowered, prolonged chemotherapy throughout the winter would be of doubtful value against this organism

The possible harmful effects of preventive chemotherapy must be carefully weighed against the dangers of the disease Only short courses of sulfonamide therapy—often as little as a single dose—are required to clear meningococci from carriers in order to control a potential epidemic in an institution or family More risk would be involved in a longer course (as over an entire winter) to prevent disease in a single individual

Continued oral administration of sulfonamides over a period of months as is necessary to prevent streptococcal infections of the respiratory tract in patients who have had rheumatic fever, requires careful observation of the patient for toxic effects Penicillin given by the same route has fewer toxic manifestations and is even more effective though the cost is greater The daily use of penicillin orally or by inhalation to decrease the number of respiratory organisms may often be continued safely for months with less fear of reaction, in this way the opportunity for reinfection of pharyngeal or peribronchial tissues following a virus infection of the respiratory tract is reduced As a general rule, prophylactic doses of the drugs are much smaller than therapeutic doses

Continued prophylactic administration of chemotherapeutic agents may alter the normal flora of the pharynx and gastro

* See also Chapter 5

lesions than after treatment with penicillin The edema begins to subside in two to three days the dose might then be decreased but therapy should be continued through four to six days

In animals streptomycin is more effective than penicillin Limited experience with this drug in human cases of anthrax has indicated that a dose of 0.5 Gm given intramuscularly four times a day is satisfactory

The disease is transmitted by spores of the organism (*Bacillus anthracis*) which are relatively resistant to chemotherapy 10 units of penicillin per cc is required to inhibit the growth of even small numbers of spores The bacillary form of the organism is more susceptible but bacteriostasis is seldom achieved with concentrations of less than 2.5 units of penicillin per cc The recommended doses of penicillin will not be likely to achieve blood concentrations which exceed the in vitro level of susceptibility Furthermore the bacillary form produces penicillinase, an enzyme which rapidly destroys the antibiotic hence, if a prompt clinical response is not obtained in forty eight hours the total daily dose may have to be increased to 2 000 000 units given on a two hour schedule In vitro susceptibility tests indicate that the bacillary form is inhibited by 1 μg of aureomycin 12 μg of chloramphenicol 1 μg of terramycin and 12 μg of streptomycin per cc These levels can be achieved in blood with the doses recommended

The recommended doses of sulfonamide should achieve blood levels of 7–10 mg per 100 cc

Immune Therapy

An antianthrax horse serum has been prepared commercially Serum therapy should be added to chemotherapy if the latter fails to control the edema by the third day of administration Immune therapy may also be useful from the start of therapy in very toxemic patients, especially those with positive blood cultures

The dose is large—50–100 cc given intravenously every eight hours for the cutaneous form of the disease, in cases with positive blood cultures the dose should be 150 cc per injection The total amount required will range from 200 to 2200 cc If a favorable response (indicated by decrease in edema around the area of the pustule) is promptly obtained the intramuscular route may be substituted for the intravenous injections Intramuscular injection often is painful, however

Serum sickness has almost invariably followed use of the serum

Special Measures

The pustule and surrounding local area of edema and cellulitis should not be disturbed during the acute inflammatory stage No chemotherapeutic agents or antiserum should be injected locally, interference with the body s attempt to wall off the infection invariably results in rapid spread of the disease Wet dressings of a saline solution containing 1000 units of penicillin per cc may be of some aid in causing the local lesion to heal more rapidly

After the edema has begun to subside the necrotizing action of the bacteria and its products may cause pus to form this will require surgical drainage Chemotherapy should be continued until the local lesion has healed

PREVENTION

No effective vaccine has yet been introduced The disease is occupational with tanners glovers herders and agriculturalists

Local application of antiseptics such as tincture of iodine or cauterization with phenol after known exposure has not been effective in preventing the disease

6. Bacterial Infections

GEORGE T. HARRELL

SUPPORTIVE therapy has been discussed in Chapter 5, the principles advocated should be applied to each of the following diseases Any special supportive measures will be outlined with each disease The dosage schedules for specific measures suggested in the following sections are those for a 70 Kg (156-lb) man who has been in good health before the onset of the acute infection Dosage schedules for children and for unusually large or small adults should be adjusted by the usual weight ratios If the patient is debilitated, larger doses of specific therapeutic agents may be necessary, greater attention must be given to supportive measures and nursing care

Chapter 4, on the sulfonamides and antibiotics, and Chapter 3, on immunology, further amplify many of the topics discussed here

Anthrax

SPECIFIC THERAPY

Chemotherapy

The drug of choice for cutaneous anthrax at the present time is penicillin it should be given intramuscularly—60 000 units of the aqueous solution every three hours (or 600 000 of procaine penicillin once daily) If the local lesion is secondarily infected sulfadiazine should also be administered orally, a priming dose of 4 Gm being followed by 1 Gm every four hours day and night Sulfathiazole in identical doses has been reported to be slightly more effective than sulfadiazine but may not be readily available When the edema begins to diminish (usually within one to four days), the sulfonamide might be stopped and the dose of penicillin halved Treatment should be continued until two negative cultures have been obtained or until the edema has subsided this may require ten to fourteen days

The same dosage schedule is apparently effective in cases with positive blood cultures (on occasion the bacilli can be seen directly in blood smears), or in the intestinal form of the disease which follows the ingestion of infected meat

Limited experience in the cutaneous form of the disease with the newer orally administered antibiotics has indicated that aureomycin (0 5 Gm every four hours) chloramphenicol or terramycin (0 75 Gm every six hours) are also effective The organisms disappear more slowly from the

weeks Two or three courses of antibiotic therapy may be required Chronic cases usually respond better if chemotherapy is combined with active immune therapy since the organisms are partially protected from the chemotherapeutic agents by their intracellular position

Immune Therapy

A polyvalent antiserum of bovine origin has been prepared against strains of *Br abortus* and *Br melitensis* It has been administered in six daily intravenous injections of 50–60 cc each If commercial antiserum is not available convalescent serum of high agglutination titer (1 2560 or above) may be used intravenously in toxemic patients or intrathecally in patients with meningitis Antiserum has limited effect if the agglutinin titer in the patient s blood is already elevated (1 640 or above) Its effectiveness is also decreased if the infection has been present seven months or more

Patients with chronic brucellosis are often extremely hypersensitive to any fraction of the bacteria Small doses of antigen may be given intramuscularly for desensitization Great harm can be done if the dose is too large so that a shock reaction is obtained A dilute solution of the antigen (for example brucellergin in a 1 10 000 or 1 100 000 dilution) should first be injected intradermally as a trial skin test The test area should be observed over a period of three days and the initial dilution of brucellergin brucellin or vaccine used should depend on the degree and duration of the cutaneous or systemic reaction If the patient has febrile reactions to a dilution as great as 1×10^{6} (1 1 000 000) desensitization therapy will probably do more harm than good *

In some cases a vaccine containing whole organisms of the strain with which the patient is infected gives better results than the soluble products (brucellergin and brucellin) In extremely hypersensitive individuals an oxidized vaccine similar to that prepared with *Pasteurella tularensis* should be used The diluted vaccine should be administered subcutaneously or intramuscularly at intervals of two to five days no injection should be given if a residual area of soreness persists from the preceding one The size of the dose and the strength of the material used should be gradually increased as the patient s tolerance permits At least two months is usually necessary for a bactericidal effect to be observed and injections may have to be continued for as long as a year

Supportive Therapy

Because of the pronounced sweating which occurs the fluid and mineral balance must be carefully maintained In the chronic form dietary measures are important Many patients especially those with the chronic form of the disease which has not localized in a particular organ have innumerable complaints Sympathetic psychiatric care is needed

Treatment of Complications

Subacute bacterial endocarditis meningitis osteomyelitis and other localized infections may follow the acute septicemic stage Treatment with aureomycin in oral doses of 0 75 Gm every six hours is combined with 0 5 Gm of dihydrostreptomycin given intramuscularly every six hours (or 1 Gm every twelve hours) the period of treatment should be at least twenty eight days unless toxic reactions to streptomycin appear

Special Measures

In cases of meningitis intrathecal injections of immune or convalescent serum may be required Excreta should be sterilized *

* See also Chapter 24

* See also Chapter 20

Brucellosis

SPECIFIC THERAPY

Chemotherapy

Though information on long term follow ups is inadequate at this time, the treatment of choice in acute infections with blood cultures positive for *Brucella abortus, Br melitensis*, or *Br suis* seems to be aureomycin The drug is given in oral doses of 0 5 Gm every six hours for a period of fourteen days Because of severe Herxheimer like reactions which have been observed in infections with the *melitensis* strain, it is probably wise to begin treatment in that infection with a total dose of 0 1 Gm on the first day increasing the dose to 0 6 1 6, and 2 0 Gm on succeeding days These amounts are given in divided doses on a six hour schedule After the fourth day the dose should be 0 5 Gm every six hours through the fourteenth day Clinical relapses occur in a small number of cases, a second course of the drug is usually effective in ten days

In a smaller number of acute cases chloramphenicol has also been reported to be effective The initial oral dose of 50 mg per kg body weight is given in broken doses hourly for three hours (approximately 1 Gm every hour for a total of 3 Gm) Subsequent doses are 0 5 Gm every six hours until the temperature has been normal for at least seven days the fever usually subsides on the third day of administration Blood levels in the range of 18–50 µg per cc are achieved on the second day of treatment with this dosage schedule If relapse occurs a second course of 3–4 Gm daily for ten days should be administered

More recently terramycin has been reported to be effective in acute cases The drug is given orally on a four hour schedule in a total daily dose of 0 1 Gm per kg body weight until the fever subsides—usually by the third day The dose is then halved, but the drug is continued for twenty eight days Febrile exacerbations have been observed on the day therapy is initiated Relapses occur

If aureomycin chloramphenicol, or terramycin is not available, acute infections with the *abortus, suis*, or *melitensis* strains should be treated with a combination of dihydrostreptomycin and sulfadiazine Dihydrostreptomycin (or streptomycin) should be given intramuscularly in doses of 0 5 Gm every six hours for fourteen days, this dose will achieve blood levels of 15–20 µg per cc Sulfadiazine should be given orally, a priming dose of 4 Gm being followed by 1 Gm every four hours for three weeks, this dose will achieve a blood level of 7–10 mg per 100 cc

All three species of *Brucella* are inhibited in vitro by aureomycin in concentrations of 0 4–1 4 µg per cc 50–100 µg per cc are required for a bactericidal effect *Br abortus* is inhibited by 2 µg per cc of chloramphenicol the *suis* and *melitensis* species are inhibited by 0 5 µg per cc A streptomycin concentration of 2 µg per cc inhibits all species in vitro 5 µg per cc is bactericidal Terramycin in concentrations of 0 4–1 6 µg per cc inhibits all species The most accurate method for in vitro testing of susceptibility employs fertile hen s eggs as the test medium Some strains of the organism develop streptomycin fastness of high degree in several weeks, this tendency is much less marked with aureomycin

In chronic cases of brucellosis (three months' duration or longer) the dosage schedules outlined for acute infections should be followed, but the drugs will probably have to be given for at least four

handled by clinical observation of the blood pressure pulse and state of hydration

If possible the blood chlorides and carbon dioxide combining power should be followed since acidosis may result from the loss of base In extremely severe cases a hypertonic solution containing 13 75 Gm of sodium chloride and 0 25 Gm of calcium chloride in 100 cc of water may be used As much as 50 Gm of sodium chloride may be required in twenty four hours

In cases of shock which do not respond to replacement of salt and water hypertonic glucose in a 25-50 per cent solution may be given but the total amount should not exceed 300 Gm daily Patients do not need plasma unless they are quite malnourished

The acute phase of cholera usually lasts four to five days As soon as vomiting has stopped water and tea may be given by mouth Because of the short course of the disease, it is not necessary to force food

The severe abdominal cramps may require regular administration of morphine Atropine given by hypodermic injection or tincture of belladonna given by mouth in maximum doses will also decrease the number of stools Preparations containing kaolin tend to absorb the endotoxin and to decrease the fluidity of the stools

SPECIFIC THERAPY

Chemotherapy

Chemotherapy is simply an adjunct to fluid replacement in the treatment of cholera The sulfonamides are the drugs of choice at the present time The effectiveness of any drug is lessened by the extreme diarrhea and by vomiting Since the organism does not penetrate beneath the mucosa of the intestinal tract a high concentration of the chemotherapeutic agent in the lumen of the bowel is essential for this reason succinylsulfathiazole or sulfaguanidine (both of which are poorly absorbed) would be the preferred forms if they are available An initial dose of 5 Gm should be followed by 2 5 Gm every four hours until the stools have been reduced in number to less than two a day Clinical improvement has been reported within three to four hours, and cultures have been reported to become negative within eight hours This dose will achieve a concentration in the stool of 25-40 mg per 100 cc In vitro concentrations of 0 2 mg per 100 cc of succinylsulfathiazole inhibit the organism and levels of 20 mg are bactericidal Sulfaguanidine is bacteriostatic at a level of 0 2 mg per 100 cc and bactericidal at 100-200 mg per 100 cc In a limited clinical trial another poorly absorbed sulfonamide, phthalylsulfacetimide (thalamyd) has been effective The initial dose of 5 Gm is followed by 1 Gm every two hours day and night for five days

If sulfadiazine is used, 1 Gm should be administered orally every four hours, day and night This dose will achieve a concentration in the stool and blood of 3-6 mg per 100 cc If the patient is vomiting the initial dose could be given intravenously as 50 cc of the 5 per cent solution subsequently the oral route can be used Stool cultures are usually positive for eight days on this regimen Because of the extreme dehydration of the patients the urine must be very carefully watched for red blood cells or crystals if they appear sulfonamides should be discontinued

Streptomycin administered orally, 4 Gm per day, is about as effective as sulfadiazine In vitro, the organism is susceptible to 2-5 μg per cc

Chloramphenicol in concentrations of at least 5 μg per cc inhibits the organism in vitro No data are available on the clinical effectiveness of aureomycin and chloramphenicol these antibiotics may prove to be superior to the sulfonamides

TREATMENT OF CARRIERS

The bacilli frequently localize in the gallbladder, where they not only maintain hypersensitivity of the patient and produce symptoms, but also serve as a focus for excretion in stools. Streptomycin has been found in material obtained by duodenal drainage, aureomycin has not been recovered. Combined therapy with sulfadiazine and dihydrostreptomycin should be tried, and the effect evaluated by cultures taken through a duodenal tube. The doses necessary are probably smaller than those described under acute infections, but treatment may have to be continued for a longer period. Surgical removal of the gallbladder is usually necessary to eradicate this carrier state, but should be delayed until chemotherapy has been instituted.

PREVENTION

Only pasteurized milk and dairy products should be consumed. Animals used as milk producers or intended for slaughter as food should be destroyed if evidence of infection is found. Herds should be regularly tested for Bang's disease.

The value of prophylactic vaccine in the prevention of the disease is still controversial. Mixed vaccines containing 1000 million heat killed organisms of both *Br abortus* and *Br melitensis* have been used. Subcutaneous injections of 0.5, 1.0 and 1.c cc should be given at weekly intervals, and the course should be repeated yearly. It would seem worth while to administer the vaccine to packing house workers, veterinarians, dairy farmers, and laboratory workers who handle cultures of the organisms or infected experimental animals.

Cholera

SUPPORTIVE THERAPY

Fluid replacement therapy is the most important phase of the treatment of cholera. The endotoxin of the organism appears to alter the permeability of the intestinal mucosa and capillaries so that fluid and salts are lost from the blood in tremendous quantities. Patients who are not comatose or in shock should be given 1 per cent sodium bicarbonate, normal saline, or sixth molar sodium lactate solution orally in amounts of 50–100 cc every half hour, at least 3–5 L per day should be administered.

If the patient is in coma or shock fluid must be administered intravenously as an emergency measure. If a vein cannot be located promptly with a needle an incision should be made and a cannula inserted directly into one, or fluids should be given through a special needle inserted in the bone marrow. A warmed solution o normal saline (or lactate Ringer's solution should be given at the rate of 60–100 cc per minute. Most patients will require 2 L every six to eight hours for the first tw days.

The amount of fluid necessary may b estimated from the specific gravity of th blood, determined by the copper sulfat method* every four hours. The specifi gravity normally 1.056 may rise as hig as 1.070. A useful guide is to give 1000 cc of fluids for a reading of 1.062, increasin the amount by 500 cc for each 0.001 increase in specific gravity. 2500 cc is th maximum which should be given at on time. Determinations of the hemoglobi or hematocrit level may be used if th copper sulfate solutions are not available. Most cases, however, can be satisfactoril

* See Chapter 48

of cultures may allow the development of serious complications

The minimum initial dose is 20 000 units in a single injection the dose should be adjusted upward to 150 000 units depending on the clinical severity of the illness and the size of the patient The intramuscular route of administration is usually adequate in severely toxemic patients it may be wise to administer the first 20 000–40 000 units intravenously and the remainder of the initial dose intramuscularly Further intramuscular injections of 20 000–60 000 units may be necessary on successive days, if improvement does not occur rapidly Since circulating toxin must be completely neutralized and since an excessive amount of antitoxin does no harm it is better to waste some material than to give it in inadequate doses

If a skin test shows the patient to be sensitive to antitoxin the serum should not be withheld, but the patient should be rapidly desensitized and a full therapeutic dose administered as quickly as is feasible Desensitization usually can be started with the subcutaneous administration of 0 1 cc of a 1 100 dilution (or 1 10 if the skin test is only slightly positive) The dose can be doubled every twenty minutes until 1 cc of full strength antitoxin has been given The intracutaneous injection of 0 2 cc of 1 1000 epinephrine solution and the oral administration of antihistaminics will lessen the likelihood of an anaphylactic reaction

In cases when laryngeal involvement is suspected antitoxin should not be administered in the home The edema produced by the antigen antibody reaction may precipitate suffocation requiring emergency tracheotomy *

Chemotherapy

Chemotherapy is simply an adjunct to immune therapy with antitoxin It should be started as soon as the diagnosis is suspected, however, since it does decrease the number of organisms present in the acute infection, shorten convalescence and prevent or eradicate the carrier state, it may also prevent complications such as lymphadenitis and otitis

Penicillin is the drug of choice, and should be given intramuscularly in a dose of 40 000 units of the aqueous solution every three hours day and night (or 300 000 units of procaine penicillin once daily) for at least six days if the membrane has not disappeared and epithelization of the infected area is not complete at the end of that time, the drug should be continued for four more days

The *Corynebacterium diphtheriae* is only moderately susceptible to penicillin sulfonamides are ineffective against it In vitro it is susceptible to penicillin in concentrations of 0 5–1 5 units per cc Since little information is available on the difference in susceptibility of the *gravis*, *intermedius*, and *mitis* strains it might be wise to increase the total daily dose to at least 750 000 units in infections with the *intermedius* or *gravis* type

Since the organism grows in the dead cells and exudate of the membrane, parenterally administered chemotherapy may not reach it in an effective concentration Local application of penicillin by nose drops or spray to the nose and throat might be used as an adjunct to parenteral therapy but should not be depended upon alone One cc of a saline solution containing 10 000 units per cc should be used every two hours this solution may tend to inactivate toxin already formed and not yet neutralized by antitoxin

In skin or vulvar infections compresses or irrigations with a saline solution containing 1000 units of penicillin per cc are helpful

Treatment of Complications

All complications should be watched for, even in clinically mild cases

* See Chapter 36

Special Measures

Stools and vomitus should be collected and sterilized Most patients have fecal incontinence and will involuntarily contaminate bedding and linen Since the disease occurs in epidemics, adequate nursing care is rarely available A convenient means of meeting this problem is to stretch a pallet across two saw horses or trellises a hole is cut in the center and the patient placed so that his buttocks cover the hole Defecation can take place in the sitting or recumbent position and stools can pass directly into a vessel containing 1 per cent cresol or some other antiseptic

Isolation of stools should be continued for ten days after the diarrhea has stopped

Treatment of Complications

The extreme dehydration and shock may lead to suppression of urine Even when this is complete the administration of sulfadiazine has not been reported as harmful If resumption of urine flow can be induced by fluid replacement within forty-eight hours the patient will usually recover If anuria continues beyond the second day of fluid replacement therapy the case should be handled as one of lower nephron nephrosis *

Renal function may be permanently impaired, the extent of damage should be determined by function tests six months after recovery

Pneumonia and parotitis should be treated with penicillin

* See Chapter 18

TREATMENT OF CARRIERS

In most cases regardless of the type of therapy, the stools become negative within seven to ten days Almost all carriers are free of organisms in one month without therapy The administration of sulfonamides or streptomycin has not shortened the duration of the carrier state

PREVENTION

All water or other liquid ingested should be boiled Stool cultures should be done on food handlers, and all foods should be cooked before being eaten

A vaccine containing 8000 million organisms per cc offers some protection The initial dose of 0 5 cc should be followed in seven days by an injection of 1 cc. The duration of immunity is so short that it is necessary to administer a booster dose of 1 cc every four to six months

In endemic areas water supplies may be treated by the addition of a bacteriophage against the specific endemic strain This measure has been reported to be helpful, but is probably impractical

Diphtheria

SUPPORTIVE THERAPY

Because of the late development of some complications bed rest is essential until convalescence is far advanced Activity should be restricted for at least four weeks

Because of a tendency toward hypoglycemia, the diet should contain adequate carbohydrate—about 250 Gm daily Some authors believe that the daily administration of 0 1 Gm or more of ascorbic acid may compensate for any damage to the adrenals

SPECIFIC THERAPY

Immune Therapy

Antitoxin should be administered as soon as the disease is suspected clinically A few hours' delay in waiting for the report

least twelve times daily may be helpful, however, local therapy alone should not be depended upon to eradicate the carrier state

In most instances, if the organisms do not disappear within two weeks after penicillin therapy is started, a tonsillectomy (with or without subsequent roentgen irradiation of the nasopharynx) will be necessary

On occasion the intramuscular administration of a single dose of 10,000 units of antitoxin seems to be a helpful adjunct to chemotherapy, even though the patient theoretically should already have adequate circulating antitoxin In other instances the administration of fluid toxoid in repeated small doses is of aid, especially in those individuals who show a pseudopositive Schick reaction * The initial dose should be judged on the basis of the degree of reaction to the Schick test material

The carrier state should not be considered as eradicated until four consecutive cultures have been negative, three should be taken at forty eight hour intervals, and the fourth one week after the third In obtaining the material for culture, swabs should be taken from high in the nasopharynx as well as from the throat

PREVENTION

Active immunization is best performed at about the age of six months Two 0 5 cc doses of alum precipitated toxoid should be given intramuscularly, with a four week interval between An equally good immune response is obtained if the toxoid is combined with antigens against other diseases such as tetanus, whooping cough, and typhoid fever †

In older children or young adults the fluid toxoid gives fewer local reactions than the alum precipitated form, it should be given in doses of 0 5 cc once a month for three months If the individual gives a very strong positive reaction to the Schick test, it would be better to give the toxoid in doses of 0 1, 0 3 and 0 5 cc respectively

In older adults the mixture of toxin antitoxin seems to cause fewer immediate reactions although it may sensitize the patient to horse serum The dose is 1 cc weekly for three weeks

Infections with the *gravis* strain may not be completely prevented by immunization with ordinary materials The exact immunologic relationship of the *gravis, intermedius,* and *mitis* types is still not clear

The degree of immunity obtained should be determined by a Schick test six months after the completion of immunization The reaction is observed at seventy two hours, at this time it has reached its height, though it may persist for several more days A pseudoreaction, apparently caused by sensitivity to proteins in the bacterial body (or to the toxin itself), is not indicative of inadequate circulating antitoxin the pseudoreaction reaches its height at about twenty four hours and usually subsides before a true reaction would appear It is accompanied by a positive reaction to the simultaneously injected control solution

Since the incubation period of diphtheria is from two to five days, prophylactic passive immunization can be conferred on a patient who has been exposed and whose Schick reaction is unknown A single intramuscular injection of 10 000 units of antitoxin is usually adequate In case of exposure to the *gravis* strain the dose should be increased to 20 000 to 40 000 units The patient should receive a Schick test six months after the prophylactic injection of antitoxin a test done at the time of administration will be obscured by the injected antibody

Prophylactic chemotherapy has not yet been shown to be of any value

* See *Chapter 48*
† See also Chapter 3

Asphyxia resulting from occlusion of any part of the airway by the membrane must be treated with immediate surgical intervention and the administration of oxygen. A tracheotomy or laryngeal intubation set should be immediately available at all times, preferably at the bedside. Aspiration of the pharynx or trachea must be frequently repeated after a tube is inserted; a special nurse is almost imperative.*

Otitis, cervical lymphadenitis, and *peritonsillar abscess* may immediately follow the acute disease. Incision and drainage should be postponed until diphtheroids and beta hemolytic streptococci (which are frequently present) are eliminated from the throat, or greatly reduced in number.†

During early convalescence *paralysis of motor nerves* to the palate and pharynx may be manifested by a change in the character of voice sounds or by difficulty in swallowing liquids; fluid is noted to run out the nose. In cases of nasopharyngeal paralysis the patient should be fed through a stomach tube to prevent the development of aspiration pneumonia.

From the third to the eighth week ocular paralysis—strabismus, pupillary inequality, or blurring of vision—or peripheral neuritis may be noted. If the muscles of respiration—especially the intercostal muscles and diaphragm—are involved, it may be necessary to place the patient in a respirator. No specific therapy is indicated for the neuritis, since the antitoxin titer of the blood is already high. Muscle stimulation, the administration of thiamin, and other measures described in chapters on neuritis and poliomyelitis should be followed.‡ Recovery from peripheral neuritis may take months.

Myocarditis may appear early in the course, during the acute febrile stage; additional antitoxin is then indicated. More commonly it appears in the third or fourth week during convalescence, frequently with no warning or premonitory sign. The only treatment is rest—as complete as possible. Since a myocardium damaged by infection is more sensitive to digitalis than one failing as the result of a mechanical (valvular) defect, digitalis should be withheld unless frank congestive failure develops. If the patient survives the first few days of the attack of myocarditis, recovery is usually complete. Resumption of full activity must be carefully governed by repeated clinical and laboratory (electrocardiogram) examination.*

* See also Chapter 36.
† *Ibid.*
‡ See Chapter 20.

Special Measures

An ice collar frequently replenished will often alleviate pain and reduce swelling of the neck. Steam inhalations from a croup kettle have a soothing effect and tend to loosen the membrane. Local irrigation of the pharynx with saline, hydrogen peroxide, or sodium perborate may be cautiously used; irrigation should never be employed in comatose patients or in those who are having difficulty in breathing. Gargles should not be used, since infected material may be aspirated or forced into the ears.

TREATMENT OF CARRIERS

All physicians, nurses and auxiliary personnel employed in nurseries or on pediatric wards should be examined for the presence of diphtheroids before they are allowed to begin work. The virulence of strains recovered from the nasopharynx of carriers should be established before therapy is instituted.

Treatment is best started with the intramuscular injection of 30 000 units of an aqueous solution of penicillin every three hours for twelve days. In children the dosage can be calculated on the basis of 10 000 units per kg. body weight per day. In addition to parenteral penicillin, the use of a solution of 10 000 units per cc. as a spray to the nose and throat (or as nose drops) at

* See also Chapter 10.

per day on a six hour schedule for six days is usually adequate

In the absence of supplies of succinylsulfathiazole, sulfaguanidine is satisfactory in a dose of 3 5 Gm every four to six hours day and night until the stools have decreased in number to less than five per day *Sulfaguanidine will* cause more reactions in the patient than the other poorly soluble sulfonamides With these drugs it is advisable to continue therapy until the proctoscopic examination reveals a normal mucosa, and until the stool cultures are negative

Patients who have not responded to sulfonamide therapy in two days may be infected with a sulfonamide resistant strain (usually *sonnei*) Antibiotic therapy should then be administered, it should be used in patients who have idiosyncrasy to sulfonamides Extreme dehydration or renal damage which would be aggravated by sulfadiazine therapy are other indications for antibiotic therapy

Streptomycin in doses of 0 5 Gm every four hours by mouth for seven days has been very effective The temperature drops in twelve to twenty four hours, and the cultures become negative by the second day This dose will produce a local concentration which exceeds the in vitro susceptibility of the *Shigella* organisms (7 μg per cc)

Chloramphenicol in a dose of 60 mg per Kg body weight daily on a four hour schedule has been effective In most children a dose of 250 mg by mouth every four hours for eight to ten days is satisfactory These doses will achieve blood levels in the range of 6–12 μg per cc The in vitro susceptibility of *Shigella* organisms is 3–6 μg per cc Cultures usually become negative by the second day Aureomycin is also effective but *is not tolerated as well as* chloramphenicol in the presence of diarrhea

Stool cultures should be checked three weeks after completion of therapy

Immune Therapy

Most strains of *Shigella* produce an endotoxin which is released as the organisms disintegrate The *dysenteriae* (Shiga) strain appears to produce in addition a soluble exotoxin A serum has been prepared in horses which has a high antitoxin titer but little antibacterial activity It should be used only in severely toxemic patients infected with the *Shiga strain, it is useless* after the seventh day of the disease The dose is 40–80 cc., usually given intramuscularly While it may be given intravenously diluted in 500 cc of saline, fewer reactions *occur with the intramuscular route* The dose is repeated every twelve hours until a clinical response is obtained If the serum is effective, a definite lessening of toxemia and drop in temperature will occur in a matter of hours after the injection

In epidemics a type specific bacteriophage may be prepared for oral administration Polyvalent stock strains of bacteriophage are usually useless

Special Measures

Rubber gloved isolation should be used and all fecal discharges should be sterilized

Treatment of Complications

In severely ill patients peripheral circulatory collapse may develop The collapse is usually due to dehydration and will respond to the intravenous administration of saline, sodium lactate, or glucose solutions Plasma is rarely necessary except in severely debilitated or malnourished persons

Other complications have been greatly reduced by the introduction of chemotherapy Occasionally perforation and peritonitis will develop or, in the most severe cases, gangrene of the bowel, immediate surgical intervention is usually required Arthritis affecting the knee or ankle may develop between the sixth and twenty third days no specific treatment is necessary My

Dysentery (Bacillary)

SUPPORTIVE THERAPY

The patient should be kept at absolute bed rest until the acute symptoms have subsided

The diarrhea, which is often accompanied by vomiting may lead to severe dehydration Fluids should be forced by mouth or parenterally in sufficient quantity to insure a urine volume of at least 1500 cc. per day Since most cases of dysentery occur during warm weather or in tropical climates, the patient sweats a great deal and loses fluid and salt in this fashion as well as through fecal discharges The loss of base exaggerates the tendency toward acidosis, so that sodium lactate or sodium bicarbonate may be necessary in addition to saline These principles are discussed in greater detail under Cholera The diet should be soft and bland

Abdominal pain may be severe enough to require opiates Morphine stops diarrhea by inhibiting peristalsis in the contraction phase atropine which interrupts peristalsis with the muscles in relaxation is preferable since it improves the blood supply to the submucosa this point is especially important if antiserum is being given since it is desirable to have the antibodies present in high concentration at the site of localization of the organism

SPECIFIC THERAPY

Chemotherapy

The drugs of choice at the present time are the sulfonamides The clinical picture of dysentery may be caused by a wide variety of gram negative bacilli not all of which fall within the *Shigella* species hence, a drug with a moderately wide therapeutic spectrum is desirable The *para dysenteriae* (Flexner Hiss and other) strains are quite susceptible to sulfonamides the *sonnei* (Sonne) strains are more resistant. Before the introduction of chemotherapy the mortality ranged from 2 to 5 per cent in most series of cases, in epidemics due to the *dysenteriae* (Shiga) strain the fatality rate has been as high as 25 to 50 per cent The use of chemotherapy has reduced the mortality to a negligible figure

Since the organisms produce systemic manifestations by invading the layers of the bowel below the mucosa a soluble sulfonamide would be preferable during the acute stage Sulfadiazine given orally in doses of 1 Gm every six hours is usually adequate The acute symptoms of dysentery appear after an incubation period of twelve hours and usually last two to six days It is advisable to begin sulfadiazine therapy as soon as practicable after the onset of symptoms and to continue it for two days after clinical recovery the drug should be administered for at least four days The cultures are usually negative after two days Because of the dehydration resulting from diarrhea, the blood level may exceed 8 mg per 100 cc, if it does, the dose should be reduced after forty-eight hours of treatment

The less soluble sulfonamides which maintain a high local concentration within the lumen of the bowel, have also been widely used during the acute phase Succinylsulfathiazole in doses of 5 Gm every six hours is almost as satisfactory as sulfadiazine it should be continued until the fever and diarrhea have subsided If there is no improvement within three days, the dose should be doubled or another drug substituted In children who are the most frequent victims of dysentery in this country, a dose of 0 25 Gm per kg body weight

Gas Gangrene

SUPPORTIVE THERAPY

Since many wounds infected with gas gangrene are severely contused the crush syndrome (lower nephron nephrosis) with shock and anuria may develop The toxemia of the infection also produces tachycardia and frequently peripheral cir culatory collapse of a severe degree Re gardless of its origin the shock should be treated with transfusions of whole blood and infusions of glucose and saline

Because of the short duration of the acute disease diet is relatively unimpor tant The organisms produce their toxins in the presence of protein hence foods con sisting chiefly of carbohydrate should be used for the first three days at least Fluids should be forced Morphine should be used for relief of the pain since it will also abolish the cerebral excitement which is part of the disease

SPECIFIC THERAPY

Chemotherapy

All wounds in patients with gas gan grene have mixed bacterial flora The com mon pyogenic organisms tend to exhaust the tissue s store of oxygen which is al ready lowered by the ischemia and edema resulting from trauma The anaerobic state thus produced favors the growth of *Clos tridia* and the production of toxins The circulatory disturbance in addition to pro ducing relative anoxia interferes with the penetration of chemotherapeutic agents into the infected area

Penicillin should be given in large doses as soon as the diagnosis is suspected All strains of *Clostridia*, with the possible ex ception of *Cl novyi* (*Bacillus oedema tiens*) are susceptible in vitro to a concen tration of penicillin in the range of 0 01 nits per cc To achieve a high tissue con ckly as possible 500 000 to

1 000 000 units of an aqueous solution of penicillin G should be given intravenously subsequent doses should be administered intramuscularly in the range of 200 000 to 500 000 units every two hours day and night This dosage schedule should pro duce a blood concentration of about 4 units per cc but the tissue concentration which is the important factor is unpre dictable After five days depending on the clinical response of the patient the drug may be discontinued or given at reduced dosage (20 000–50 000 units every three hours) for an additional ten to fifteen days

In severe cases both penicillin and sulfa diazine should be given Sulfadiazine is clinically effective in reducing the bacterial contamination of the wound but has little effect on *Cl novyi* The initial oral dose should be 0 1 Gm per kg body weight the total not to exceed 5 Gm subsequen doses should be 1 Gm every four hour day and night After five days if improv ment is evident the dose may be cut half but the drug should be continued f a total period of two weeks Because of tendency of the disease to produce ripheral circulatory collapse with re shutdown the blood concentration sh not be allowed to exceed 10 mg per 10 The drug should be discontinued i guria supervenes penicillin need n discontinued since it is relatively toxic even in high concentration

Experiments in animals indicat aureomycin in maximal doses admin within four hours of the injectio definite aid Reports are not yet a on its use in human beings

Special Measures

The most important phase of th (as well as the prophylaxis) of ga is adequate surgical treatment,

ocarditis and pericarditis rarely occur, they should be treated according to the suggestions given in Chapter 10 Nephritis will occasionally follow dysentery Parotitis and terminal pneumonia, which are usually due to gram positive cocci are now infrequent, they should be treated with penicillin

Roughly 2 per cent of the acute cases of dysentery will progress to a chronic phase which often resembles chronic ulcerative colitis Usually infection with the Flexner or Sonne strains has little effect on the health of the individual infection with the Shiga strain often leads to protracted ill health Succinylsulfathiazole or streptomycin should be used in the dosages outlined above, but therapy should be continued over a period of at least ten to fourteen days Elimination diets will reduce the symptoms from food allergies that seem to develop during the course of Shiga infections, the removal of roughage from the diet and other measures discussed under Chronic Ulcerative Colitis in Chapter 17 may be helpful

TREATMENT OF CARRIERS

Dysentery is passed from individual to individual through the fecal discharges of carriers or convalescent patients Even though the organisms usually disappear spontaneously within six months carriers should be treated as soon as they are detected The bacilli are not found below the mucosa in the carrier state and hence the poorly soluble sulfonamides which will give high concentrations on the surface of the bowel are the preferred drugs The daily dosage of succinylsulfathiazole should be 20 Gm, on a six hour schedule for six days in children a dose of 0 25 Gm per kg body weight per day for six or seven days should be used If the organisms do not promptly disappear, the course should be followed by sulfadiazine, 1 Gm every six hours for five days or antibiotic therapy Streptomycin should be given orally in doses of 0 5 Gm every six hours for four days chloramphenicol is administered orally in doses of 0 5 Gm every four hours for six days

Stools should be cultured three times in the two weeks following cessation of therapy

PREVENTION

The best protection can be obtained by very meticulous supervision of food and water supplies and of food handlers

Chemoprophylaxis

Chemoprophylaxis by the administration of 0 5 Gm of sulfadiazine orally every twelve hours is apparently reasonably effective in epidemics The advisability of long continued prophylaxis as has been used in streptococcal infections, is doubtful

Immune Therapy

Vaccines have been prepared, but their value is dubious So many immunologically distinct strains of dysentery and allied bacilli are known that it is difficult to prepare a polyvalent vaccine which will give adequate protection Most vaccines contain not less than 3000 million organisms per cc including at least three strains—Shiga Flexner, Hiss or some other variety Even though a small dose (0 05–0 1 cc) is given severe local reactions usually are produced The interval between injections the size of subsequent doses and the number of doses are determined by the extent of the reaction The immunity is short lived hence booster doses should be given every three months

000 units of penicillin should be given intramuscularly every two hours and 1 Gm of sulfadiazine orally every six hours In *severely contaminated wounds* a dose approaching the therapeutic amounts outlined above should be used Chemoprophylaxis should be continued for at least five days and preferably until the wound has healed Inadequate doses may alter the subsequent clinical picture of the disease so that its recognition is difficult

Passive Immunization

Antitoxin should be prophylactically administered to patients with severely contused wounds of muscle—especially those in the buttocks or thighs—where collateral circulation is inadequate, or in areas, such as the abdominal wall, where amputation cannot be performed The intramuscular dose recommended by the manufacturers in this country (4000 units combined with 1500 units of tetanus antitoxin) is entirely inadequate, and at least two to three times this amount should be given when the wound is first treated Even doses of 16 000–150 000 units have not always prevented clinical disease Antitoxin should be combined with chemoprophylaxis

Active Immunization

Potent polyvalent toxoids for active prophylactic immunization have been prepared but their effectiveness in preventing the disease has not been evaluated clinically Measurable blood levels (0 05–2 0 units per cc) of antitoxin are formed but the amount of toxin produced in a severe wound may be so great that this degree of immunity is quickly overwhelmed

Leprosy

SUPPORTIVE THERAPY

General supportive measures such as diet, rest, and sunshine should be followed as outlined under the regimen for treatment of tuberculosis * The greatest factor in the treatment of leprosy is support of the patient s morale This will require patience *and ingenuity* If sulfones are being administered ferrous gluconate or some other form of iron should be given regularly

SPECIFIC THERAPY

Chemotherapy

The *drugs of choice* at the present time are derivatives of the sulfones The active principle to which the most commonly used drugs are broken down in the body is apparently diaminodiphenyl sulfone (DADPS) This parent substance is relatively cheap and may be given orally the most effective dosage schedule is yet to be worked out A single oral dose of 0 1 Gm is given initially six days a week and then increased to 0 2 Gm daily for an indefinite period Blood levels of 0 3–0 5 mg per 100 cc are achieved on the smaller dose and 0 6–0 8 mg on the larger one

Other orally administered sulfones are more expensive but may prove to be better tolerated 'Diasone should be taken by mouth during meals or one hour afterwards The initial dose of 0 3 Gm is given *once a day for two weeks and is then* increased by 0 3 Gm every few weeks until a maximum of 0 9 Gm (1 tablet three times daily) is reached Blood levels in the range of 1 mg per 100 cc may be achieved with this dosage Following a two months

* See Chapter 16

as quickly as possible Infection by the gas producing bacilli develops in isochemic areas where arteries are damaged and collateral circulation is inadequate, and in areas where local contusion has produced edema compression of small vessels and interference with capillary flow Muscles die if deprived of their blood supply for six to eight hours Spores of the anaerobic organisms are carried into the wound on clothing especially wool hence infection of devitalized muscle may follow an injury sustained in civilian life as well as in battle Cases have even been reported following accidents on an airplane or on shipboard

The wound should be completely debrided of devitalized tissues and left open The introduction of chemotherapy and immune therapy is altering the older concept that amputation of an extremity is imperative as soon as the diagnosis of gas gangrene is made the competency of the collateral circulation will determine the necessity for amputation

After debridement Dakin s tubes may be inserted and irrigated every two to three hours with a freshly prepared solution of hydrogen peroxide (1 per cent) Dakin s solution or some similar oxidizing agent Every effort should be made to increase local vasodilation by drinks of hot fluid or small amounts of alcohol or by regional sympathetic block with procaine Tobacco should be withheld because of its vasoconstrictive effect No hot compresses should be used since they increase tissue metabolism in order to reduce the local demand for oxygen the part may be packed in ice No constricting bandages or casts should be applied though traction is permissible Restorative and corrective surgical measures should be postponed until after recovery

If treatment is to be effective some improvement will usually be noted within twenty four hours Most patients die or begin to recover within twenty four to seventy two hours The prognosis is worse in injuries involving the muscles of the thigh and buttock than in those affecting other muscles The prognosis is extremely poor in infections which have spread to the liver or blood stream from a ruptured appendix or an infected abortion The mortality in fulminating cases regardless of the site of infection is 30 to 60 per cent

Immune Therapy

A bivalent antitoxin containing 20 000 units per ampule has been prepared and is effective against *Cl perfringens* (*Bacillus welchii*) and *Cl septicum* (*Vibrion septique*) The British ampule contains 16 500 units and is effective against *Cl novyi* in addition Severely ill patients especially those showing tachycardia and icterus should be given an intramuscular dose of 3–6 ampules this dose should be repeated twice after four to six hours if necessary, and then once each day for at least four days The titer of antitoxin after a dose and the rate of disappearance from the serum are highly variable Many authors believe that antitoxin is of greater value in prophylaxis than in treatment

PREVENTION

Surgical Measures

The best method of prevention is immediate complete debridement of any open wound within the first few hours * The wound should be sutured and a cast applied if it is indicated for the treatment of a fracture If all devitalized tissue is removed and adequate circulation to the muscle is maintained gas gangrene rarely develops

Chemoprophylaxis

The administration of penicillin and sulfadiazine is effective chiefly in reducing the number of pus forming organisms The value of chemoprophylaxis is definitely dependent upon the doses used At least 50

* See also Chapter 41

hours (a total of 2 Gm daily) have usually produced toxic reactions within four months A dose of 0 5 Gm of dihydrostreptomycin every twelve hours has produced fewer toxic reactions With either dose, definite improvement has been noted after three months—much more quickly than with the sulfones—but the improvement has stopped at that time Reasoning from the findings in tuberculosis it seems likely that the organism becomes streptomycin fast, but this point cannot be proved It would seem advisable, when initiating therapy in the lepromatous or tuberculoid type of the disease to combine the smaller dose of dihydrostreptomycin with sulfone therapy for the first three or four months

Streptomycin and aureomycin (which has been given orally in doses of 1 5 Gm daily for one year) may produce as much benefit by control of secondary bacterial invaders in ulcerated lesions as by direct action on the mycobacteria

The role of *p* aminosalicylic acid (PAS) in conjunction with other therapy of leprosy is not yet clear In tuberculosis PAS seems to delay the development of drug fast strains of *Mycobacteria* and permits the use of streptomycin in longer courses

Treatment of Complications

Painful *neuritis* occurs frequently The oral or parenteral administration of a vitamin B complex preparation which includes doses of thiamin in the range of 25 mg daily often is helpful Daily intravenous injections of 10 cc of a 10 per cent solution of calcium gluconate in seven-day courses have been reported to be helpful

Trophic ulcers which result from invasion of nerves may be handled by the method described for tabes in Chapter 39

Tuberculosis occurs very frequently in patients with leprosy Apparently the lepra bacillus by damaging reticuloendothelial tissue reduces local resistance so that invasion by *Mycobacterium tuberculosis* is facilitated Previous therapy with streptomycin for leprosy should not bar another course of the drug if tuberculosis develops the schedules outlined in Chapter 16 should be used

Leptospiral Infection (Weil's Disease)

SUPPORTIVE THERAPY

The patient should be kept at absolute bed rest until convalescence is well established as necrosis of both skeletal and cardiac muscles may have occurred Because of the toxemia of the patient, fluids should be forced to insure a daily urinary output of at least 1000 cc early in the course of the disease after the kidneys are involved in the infectious process urinary suppression may intervene *Leptospira* grow less well in an acid medium hence, it may be wise to acidify the urine (especially in patients taking fruit juices) by the oral administration, at six to eight hour intervals, of methenamine and sodium biphosphate (0 6 Gm each)

Because liver damage is a part of the disease a high-carbohydrate high protein diet has been recommended whether the damaged liver and kidneys can metabolize the extra amino groups is a moot point and the amount of protein given should be governed by the level of the nonprotein nitrogen in the blood

The prophylactic oral administration of 2 mg of vitamin K each day is wise if jaundice or a bruising tendency appears 10 mg of menadione bisulfite should be given daily by hypodermic injection

course of therapy, a rest period of two weeks should be observed

Promizole is well tolerated by the oral route The starting dose of 0 5 Gm three times daily is increased gradually after two weeks until the patient s limit of tolerance is reached Most patients can take 6–8 Gm a day without toxic reactions This dose will achieve blood concentrations of 1–2 mg per 100 cc twelve hours after the last dose

Sulphetrone and promacetin in doses of 3 Gm daily, tibione in daily doses of 0 2 Gm and thiosemicarbazone ('Thiacetazone) in doses of 0 15 Gm daily are other oral sulfones which apparently are effective clinically

Many patients elect promin if a choice is given This sulfone drug is administered intravenously since oral administration produces too many toxic symptoms The initial dose of 1 Gm is gradually increased each day to a maximum of 5 Gm after the drug is given daily for two weeks, the patient is allowed to rest one week In the presence of renal damage the sulfone accumulates in the blood, so that levels of 20–30 mg per 100 cc may still be present twenty four hours after an injection if such levels are discovered the drug should be stopped

The sulfones are mildly toxic to some individuals DADPS and promin' have a tendency to produce anemia by hemolysis of erythrocytes diasone may produce agranulocytosis Hemoglobin determinations and white blood cell counts as well as urinalysis with microscopic examination of the sediment should be done weekly Should rash fever or other signs of a lepra reaction supervene the drug should be temporarily discontinued Psychic disturbances may follow the use of DADPS

The sulfones are most effective in the lepromatous and tuberculoid forms of the disease they apparently are mildly bacteriostatic and act by preventing the formation of new lesions allowing the old ones to heal by fibrosis Herxheimer like febrile reactions accompanied by mild erythema may occur, especially in the tuberculoid type they are usually interpreted as indicating destruction of *Mycobacterium leprae* and are not a contraindication to further therapy Preliminary reports indicate that ACTH may control the clinical symptoms of the Herxheimer like lepra reaction and allow uninterrupted continuation of chemotherapy

Subjective improvement is slow, and is noted by approximately 25 per cent of the patients after six months, it begins most quickly with promizole, but the serologic test for syphilis (which has been used as a prognostic sign) reverts more quickly with promin Objective clinical improvement depends upon the intensity and duration of treatment which must be continued for a period of years At the end of the first year approximately 60 per cent of patients are better After two years of continuous therapy improvement is noted in 75 per cent of patients, and after three years, in nearly 100 per cent Smears from the lepromatous lesions rarely become negative in the first year, after four years of therapy about 50 per cent of the patients have negative bacteriologic tests If the sulfone can be continued for five to six years without toxic manifestations, the chance for arrest of the disease so that the patient may be discharged from the leprosarium is apparently twice as good as with any other form of therapy A few patients have taken sulfones for over nine years The chance for arrest is improved even more by this duration of therapy Relapses occur in as high as 45 per cent of patients who are not continued on therapy, this rate is reduced to the range of 4 5 per cent for those continued on therapy

The role of streptomycin in the treatment of leprosy is still not established Intramuscular doses of 0 25 Gm every three

penicillin once or twice daily Doses should not be administered which exceed 10,000–20 000 units in concentrations of 1000 units per cc Acute myocarditis may develop during the febrile stage of the disease or during convalescence, it should be treated with prolonged rest in bed Hemorrhages occasionally occur as the result of hypoprothrombinemia Large doses of vitamin K will probably not be effective in the presence of liver damage, hence, transfusions of whole blood may be necessary to furnish preformed prothrombin Occasionally multiple small liver abscesses will develop in such cases penicillin should be continued for several weeks

PREVENTION

The disease is primarily an infection of rats, which is transmitted to man through contact of the skin with contaminated water Only occasionally will drinking water be affected Rarely strains affecting dogs are pathogenic for human beings The best means of prevention is eradication of the animal reservoirs.

The value of penicillin or antiserum given prophylactically has not been established.

In several countries abroad, vaccines prepared from heat or formalin killed cultures of *Leptospira* have been used, but their value has not been established

Paratyphoid Fever (Salmonellosis)

PARATYPHOID, an infection with one of the numerous strains of *Salmonella*, is usually less severe than typhoid fever The disease is highly variable because of the wide differences in invasiveness and virulence of various strains Since some strains are susceptible to chemotherapy, the disease should be treated in the same fashion as typhoid

Pertussis (Whooping Cough)

SUPPORTIVE THERAPY

The most distressing symptom is cough The organism induces the secretion of large amounts of very tenacious mucus which collects in the throat, nasopharynx, and nose, especially in infants The action of the cilia may be paralyzed by the endotoxin, so that they are unable to move the mucus, and there may be difficulty in coughing it out Patients with moderately severe whooping cough should be kept in a well ventilated room in which moisture is provided by a croup kettle Since the disease is most prevalent in the spring and early summer, often it is safe to move less severely ill patients to a screened porch protected from drafts Here the paroxysms of coughing seem to be reduced, probably by the humidity of the air and its freedom from house dust All varieties of drugs have been used to control the cough, but none have proved to be of much value Small oral doses of phenobarbital (2 mg per kg body weight every three or four hours during the day and a slightly larger dose at night) are helpful If the child is vomiting similar doses of sodium phenobarbital should be given by hypodermic

SPECIFIC THERAPY

Chemotherapy

The drug of choice at the present time is penicillin Penicillin seems to shorten the duration of the fever and to lessen the number of relapses, but its effectiveness definitely is related to the amount given An intramuscular dose of 40,000 units given every three hours day and night has led to clinical improvement within thirty six hours Although half this amount has been effective in clearing the urine of organisms in fifteen hours and in inducing a remission in the temperature within three days, nevertheless at least 300 000 units should be given daily for seven days. It is possible that even larger doses in the range of 100 000 units every three hours will be more effective Occasionally a Herxheimer like febrile reaction may occur four to six hours after the initial dose of penicillin

The mortality in those who develop icterus (only two thirds of the patients become jaundiced) has averaged about 30 per cent, but has varied from 4 to 60 per cent in epidemics Since penicillin has had no effect on the jaundice or on the reduction in liver or kidney function, therapy must be begun as early as possible The difficulty lies in making a diagnosis in the pre icteric stage, since it is almost impossible to demonstrate the spirochetes in the blood of man by the darkfield technic Young guinea pigs inoculated with blood drawn during the first week frequently have positive darkfield tests within three days The *Leptospira* do not appear in the urine of human patients until the second week of the disease

The organism *Leptospira icterohaemorrhagiae* is moderately susceptible to penicillin in vitro For most species of *Leptospira* a concentration of 0 4 units of penicillin per cc is bacteriostatic, but occasionally as much as 5 units is required, penicillin is not bactericidal even in concentrations of 5000 units per cc. In guinea pigs treated within twenty fours after infection, blood levels of 0 2 units per cc. are effective Apparently the drug acts through a suppressive effect, and allows immunity to eradicate the infection

Sulfonamides are of no help, in some instances patients seem to be worse after their administration

Streptomycin is effective in animals and may be useful as an adjunct to penicillin and immune therapy in man Aureomycin orally is more effective weight for weight than penicillin in experimental infections in hamsters, but no reports on its use in the human disease are available at present

Immune Therapy

Daily transfusions of 500 cc of citrated blood from convalescent donors apparently are helpful, whether or not chemotherapy is used Whole blood (if it matches that of the patient) would be preferred to serum, since anemia is one of the manifestations of the disease The serum will usually have a high agglutination titer against *Leptospira*, often in the range of 1 100,000 Lysins are present in low titer as well Transfusions are often followed within a matter of hours by a chill which seems to be related to the lethal effect of the antibodies on the organisms.

An antiserum has been prepared in horses, but is not widely available To be effective, it must be given before the sixth day of the disease The initial intravenous dose of 60 cc should be repeated every six to eight hours for three to four days

Treatment of Complications

Complications occur in 20 to 25 per cent of the cases The most common ones involve the eye—iridocyclitis, optic neuritis, and uveitis No specific local measures are necessary other than dilatation of the pupil The injection of the sclera and conjunctiva so frequently seen is a part of the disease and not a complication

Meningitis occasionally occurs and may require the intrathecal administration of

of aureomycin and terramycin of 12 μg per cc. The dose recommended will achieve blood levels in this range Drug fastness does not develop as frequently or as rapidly with these drugs as with streptomycin

Growth of most strains is inhibited in vitro by *streptomycin in a concentration of* 3 to 5 μg per cc, a concentration of 15 μg per cc is bactericidal within thirty hours Streptomycin (or dihydrostreptomycin) given intramuscularly in a dose of 50 mg *per kg body weight each day on a three-*hour schedule day and night will achieve blood concentrations which exceed the bacteriostatic levels and may reach bactericidal levels Clinical reports do not agree on the *extent to which paroxysms of cough* are decreased If chloramphenicol aureomycin, or terramycin are not tolerated orally and the parenteral form of the drug is not available, streptomycin should be tried for at least five days *It should not be given for* longer than fourteen days, because of the danger of toxic reactions in the patient and the development of drug fastness by the organism

Streptomycin has also been administered by inhalation as an aerosol One gram is dissolved in 8 cc of isotonic saline solution, and 1 cc of the solution is given every three hours over a period of seven to ten minutes, *through a nebulizer attached to an oxygen* tank from which the flow is 4 to 6 L per minute In uncomplicated cases no advantage is gained over intramuscular administration, since many organisms are located *in the* interstitial tissue of the lungs In bronchopneumonia due to *H pertussis*, organisms may be found in pus in bronchioles, and the method may have some value as an adjunct to other antibiotic therapy

No data are available on the effectiveness of combinations of chloramphenicol aureomycin, or terramycin with streptomycin In vitro and in vivo tests in animals have not demonstrated antagonism between these combinations in other bacterial infections *In severe cases of whooping* cough which have not responded to other antibiotics in three days or in cases with complications streptomycin may be useful

Therapy with antibiotics has not appre*ciably shortened the hospital* stay in acute cases, but the limited evidence available indicates that the mortality rate, especially among infants and *in* cases *with complica*tions, is appreciably reduced

Sulfadiazine will eradicate pertussis organisms from the nasopharynx only, and hence is of value chiefly in the treatment of complications

In very severe cases, chemotherapy should be *combined with immune therapy*

Immune Therapy

Hyperimmune antipertussis serum with high agglutinin titer and antibacterial *action has been prepared in human* volunteers and in rabbits The rabbit serum is prepared by the inoculation of an endotoxin in addition to whole bacterial vaccine and contains an antitoxin as well as *agglutinins and other antibodies* Clinical experience has indicated that the human serum is more efficacious and very few reactions follow its administration The serum is most effective in infants and young children if given by the intravenous route For small children the dose is 20 cc, repeated at forty eight hour intervals for three doses a fourth injection may be necessary five to seven days later if a remission has not been achieved An adequate total dose must be given since less than 60 cc may not be effective In older children the serum should be used in cases complicated by pneumonia due to *H pertussis* the dose of 50–100 cc, depending upon the size of the child should be repeated once after forty eight hours

A purified and highly concentrated gamma globulin fraction of human hyper immune serum is commercially available

The diet at first should consist of six to eight small daily feedings of concentrated liquids which contain little fat these leave the stomach quickly The paroxysms of coughing and the gagging effect of the mucus induce vomiting which increases the danger of aspiration pneumonia and otitis After the cough has begun to subside and vomiting has stopped, less concentrated liquids may be added and older children may be given soft foods three times a day

It is wise to clear the nose and throat of secretions and to give some sedative before a feeding is attempted To minimize the danger of aspiration of food or vomitus infants should be fed in the recumbent position in the nurse s or mother s arms and should never be left alone during a feeding Some authorities recommend placing the infant on its side and applying suction through the nose after the feeding If eating induces a paroxysm of cough with vomiting the infant may be placed in a sitting position with the head held forward, or suspended by his feet to allow drainage of the vomitus out of the mouth and nose In such cases the patient should be fed again in half an hour if he is not too exhausted to eat If several feedings are vomited in succession liquid formula should be given by gavage since malnutrition may develop in cases of long duration

Fluids may have to be administered parenterally during the period of severe coughing and vomiting Diarrhea and acidosis occur frequently in infants, and require the replacement of salt and base

Because of the duration of the illness *vitamin supplements* especially of A, C, and D, should be increased

SPECIFIC THERAPY

Specific therapy for pertussis should be administered to all patients under 1 year of age and to any, regardless of age, in whom complications—chiefly pneumonia—develop, or who are debilitated from intercurrent disease

It is difficult to evaluate the efficacy of any form of treatment, since the disease is so variable at different ages Furthermore, most cases are treated in the home, although the statistics which have been published are based largely on the treatment of seriously ill hospitalized patients, many of whom have had complications The maximal incidence of the infection occurs at the age of 4 years The mortality in children under 4 years of age has been estimated at 10 to 25 per cent but the fatality rate for all ages is approximately 1 per cent Two thirds of the deaths occur in infants less than 1 year old and approximately one fourth of all patients under 6 months of age who contract the disease die from it

Chemotherapy

Chloramphenicol, aureomycin, and terramycin are about equally effective in controlling the symptoms of pertussis and are the drugs of choice at present Each of the drugs is absorbed well after oral administration, or may be given parenterally if the patient is vomiting Because fewer gastrointestinal symptoms follow its oral administration and because it is better absorbed from the rectum, chloramphenicol has been more widely used The oral dose is the same for all three drugs—50 mg per kg body weight daily, given on a three to six hour schedule Fever disappears on the second day in uncomplicated cases About the third day the paroxysms of cough will decrease in severity and number, and the vomiting and respiratory distress will diminish Nasopharyngeal swab cultures usually become negative by the fourth day The antibiotic should be continued for ten days however In vitro studies show that growth of most strains of *Hemophilus pertussis* is completely inhibited after twenty four hours exposure to concentrations of chloramphenicol of 8 to 10 μg per cc, and

mycin (the bacterial antagonism is greatest with chloramphenicol) must await further study

In previous years the second most serious complication was malnutrition, but improved methods of therapy are decreasing its importance Care in the selection of the diet and in the technique of feeding will usually prevent it

Otitis occurs in almost half of the complicated cases, and is usually due to the common pyogenic bacteria found in the nasopharynx, hence streptomycin and *immune serum will be of little value in its* treatment The prompt administration of *sulfadiazine in the doses outlined for* pneumonia will usually *control* the infection within two or three days The vomiting which frequently precedes otitis may require the substitution of penicillin injected intramuscularly in the doses outlined above

Atelectasis may result from the patient s inability to cough forcibly enough to evacuate a plug of tenacious mucus The patient *should* be *turned on* the *unaffected side* and treated with steam inhalations and deep breathing of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen for three to five minutes four times a day These measures will help to expand the lung Occasionally the violent cough will produce an acute interstitial emphysema or will rupture alveolar septums *so that* areas of bullous emphysema develop nothing *can be done* about these complications If the air dissects into the pleural cavity, a spontaneous pneumothorax may occur in this case the air should be removed Bronchiectasis may develop as a late complication but treatment can be *postponed until after convalescence* is *completed*

Convulsions are a serious complication in infants and usually occur during bouts of cyanosis The administration of oxygen as well as anticonvulsants *is usually helpful* Edema *of* the brain has been observed in fatal cases, but lumbar puncture offers *little relief*

Meningitis occurs infrequently, but is a serious *complication It should* be *treated* by the method described *under* ' *influenzal* meningitis ' (Chap 20) with the substitution of hyperimmune human antipertussis for antiinfluenzal serum

During a paroxysm of severe coughing petechiae occasionally appear in the conjunctivas or elsewhere as a result of the marked increase in venous pressure Occasionally the rupture of a small vein will *produce a nose bleed* The *hemorrhages* usually require no specific therapy, provided *the intake* of vitamins C and K has been *maintained*

The severity of the coughing spells may produce an inguinal or ventral hernia Adhesive strapping may be applied to prevent an increase in the size of the hernia, but surgical repair should be postponed until the patient has been well for several months

TREATMENT OF CARRIERS

Few data are available on the carrier state, since it is often difficult to differentiate relapses and reinfections from the carrier state Convalescent patients in institutions should be segregated until nasopharyngeal swab cultures by special technics are negative, cough plate methods are *not* reliable for detection On the basis of limited clinical experience chloramphenicol *seems to be the best available drug for eradication of the organisms* from carriers The dose used *is the same as* for treatment *of the actual disease*, but the duration of administration may be shortened Sulfadiazine has also been used, it has the advantage *of being much cheaper and* may be given over long periods of time with *minimal toxic reactions (The principles of chemoprophylaxis* are discussed further under ' Scarlet Fever)

for intramuscular injection A vial of 2.5 cc is said to contain the therapeutic equivalent of 25 cc of unconcentrated serum

The earlier serum is administered, the more dramatic will be the response It is impossible to evaluate accurately its effectiveness in reducing mortality, but fatality rates as low as 1.3 per cent have been reported in small series of cases The hospital stay and total duration of the disease may not be decreased appreciably A reduction in the toxemia of the patient has been reported in 70 per cent of the cases and the number and severity of complications have been decreased The chief disadvantage of the use of serum is its limited availability

Special Measures

Severely ill patients especially infants should be hospitalized and given an immediate trial on oxygen therapy The paroxysms of cough, cyanosis and respiratory distress usually are reduced in severity within a few minutes The temperature of the air in the oxygen tent should be kept in the range of 68° F the humidity about 40 per cent, and the oxygen content at 50 per cent

The mucus may have to be aspirated In small infants, postural drainage with the head in the dependent position sometimes is adequate In others especially those who are severely ill pharyngeal and nasal suction should be applied as often as is necessary The child is held in the sitting position with the head forward and the forehead supported The mucus is aspirated through a catheter with multiple perforations near the tip (No 12 French for pharyngeal suction No 10 for the nasal route), attached to a motor-driven bedside suction apparatus

Patients should be kept isolated from other children, except those who have had the disease for about three weeks

Complications

The most serious complication is *pneumonia*, which causes approximately 90 per cent of all deaths from the disease Between 10 and 15 per cent of all cases and approximately two-thirds of those patients with some type of complication will have pneumonia the case fatality rate when this complication develops is between 15 and 30 per cent The pneumonia may be interstitial in type (This form can be reproduced in animals by instilling the endotoxin of the organism into the trachea) The more common type is bronchopneumonia which is usually due to secondary invasion by gram positive cocci, though it may be caused by *H pertussis* itself The interstitial type clears more slowly than bronchopneumonia If the patient is not being given specific chemotherapy or immune therapy, both should be started as soon as pneumonic involvement is noted

If chloramphenicol aureomycin or terramycin is already being given, intramuscular injections of an aqueous solution of streptomycin (50 mg per Kg body weight daily) should be added on a six hour schedule If the patient is being treated in the home, oral sulfadiazine may be preferred the initial dose should be 70 mg per Kg body weight and the subsequent daily dose 150 mg per Kg, given on a four hour schedule day and night Penicillin would be the logical drug to administer if gram positive cocci are found, the equivocal clinical improvement noted after its administration to patients with pertussis is probably due to the control of secondary invaders rather than to any direct action on *Hemophilus* itself However, if penicillin is used with chloramphenicol, aureomycin, or terramycin, the inhibition of bacterial growth and the bactericidal action of penicillin are antagonized. The possible value of massive doses of aqueous penicillin with small doses of aureomycin or terra

istered to infants or debilitated children under 10 years of age who have not had the disease The incubation period ranges from five to fourteen days, averaging about seven days, passive immunization is of little value more than two weeks after exposure An initial dose of 20 cc should be given as soon as possible after exposure and repeated three to five days later, if exposure has been continuous or unusually intimate, a third dose should be given three weeks after the second

The duration of the exposure is apparently the most important factor in determining the effectiveness of passive immunization In epidemics occurring in institutions this technic has protected from two-thirds to three fourths of the children treated, whereas only 10 to 20 per cent of nonimmunized children escaped the disease

Chemoprophylaxis

Although sulfadiazine, penicillin, streptomycin, aureomycin and chloramphenicol have been used in treatment of the disease no conclusive data are available on their effectiveness in prophylaxis

Plague

SPECIFIC THERAPY

Chemotherapy

The drugs of choice at the present time are streptomycin and sulfadiazine The dosage schedules required vary, depending upon the type of infection and the country where it is acquired Outside the United States, plague is chiefly an infection of rats, in which the virulence of the organism is maintained at an extremely high level Seventy five per cent of the cases are of the bubonic variety fewer cases of the primary septicemic and primary pneumonic types occur, but the mortality has been 90 to 100 per cent in the latter two types In the fulminating cases the organism multiplies extremely rapidly and the disease progresses with lightning speed It is, therefore, important that treatment with maximum doses of drugs be instituted as early as possible in any type of the disease

In this country sylvatic plague is primarily an infection of wild rodents in the Pacific coast area The disease, which is *almost entirely bubonic in type* is less virulent and carries a lower mortality than murine plague Laboratory infections, though, are often of extreme virulence

Streptomycin is very active against *Pasteurella pestis*, a concentration of 3 μg per cc is bactericidal in twenty four hours and 10 μg per cc will sterilize heavily inoculated cultures within six hours Streptomycin (or dihydrostreptomycin) alone *is all* that is required in the bubonic form, as is the case in infections with *Pasteurella tularensis*

For the bubonic type, streptomycin should be started immediately in daily intramuscular doses of 2–3 Gm on a six hour schedule, this dose will achieve blood levels of 10–20 μg per cc Improvement should be noted within thirty six hours Benefit from the drug is greatly reduced if treatment is started after the third day A total dose of 8 Gm in four days is usually sufficient, even in severely ill patients

In the pneumonic and septicemic types the dose should be increased to 4–6 Gm per day, and should always be combined with sulfadiazine Streptomycin should be continued until the temperature has been normal for two days therapy with sulfadiazine should be continued for ten to fifteen days longer

Sulfadiazine should be given in large

PREVENTION

Active Immunization

All infants should be immunized with a vaccine The optimal age for immunization is still in dispute Roughly one eighth of all cases occur in babies under the age of 6 months and roughly one fourth of the infants infected before this age die Many authorities insist, therefore that injections of the vaccine should be started by the third month of life, especially in children living in crowded areas of a city or in institutions the first injection should certainly be given before the age of 7 months

The vaccine must be prepared from specially isolated organisms which exhibit growth characteristics of Phase 1 The potency of vaccines varies from 2 to 40 billion killed organisms per cc The total number of organisms administered in the entire course of immunization is the important factor Whether the plain or alum precipitated single vaccine or a combined vaccine (which includes toxoids of diphtheria and tetanus) is used the injections should be given intramuscularly at four week intervals Best results have been obtained following the injection of 40 billion organisms at monthly intervals for three doses (a total of 120 billion organisms in a plain vaccine) Satisfactory immunization has been achieved with the deep injection of 20 billion organisms contained in an alum precipitated vaccine the initial injection of 10 billion organisms is repeated after four weeks Sterile abscesses resulting from the injection occur more frequently with alum precipitated vaccines (especially if some vaccine remaining on the outside of the needle is left intradermally or subcutaneously) than with plain vaccines Either type may cause systemic reactions which increase in frequency with each additional dose

The effectiveness of immunization may be determined after four to six months by an agglutination test performed on a slide or piece of paper The patient's serum is tested against a suspension of 100 billion dead bacilli per cc More recently a skin test has been proposed for the same purpose, 0 1 cc of a solution containing 100 units of lyophilized purified agglutinogen dissolved in 1 cc of sterile diluent is injected intradermally Readings are made thirty minutes and twenty four hours after the injection The latter reading is more reliable and is more likely to be positive in immunized individuals An immune child may show either an immediate wheal like reaction or a delayed tuberculin like test, with induration greater than 10 mm in diameter (Erythema, which will also be present is not significant) Negative readings at both times indicate that immunity is inadequate and the complete course of vaccine should be repeated

Single intramuscular booster injections of 20 to 40 billion organisms should be given six months after completion of the initial course of vaccine and at 2 years of age More than half of the cases of pertussis occur in children above the age of 2 years but the mortality is much lower than in younger patients hence further injections decrease progressively in value A booster should be given at any time if an epidemic occurs in an institution, or if the child is being intimately exposed in the home

The annual attack rate in nonimmunized children has been estimated in the range of 11 per cent Vaccination has reduced the incidence of frank cases of the disease to one third or one fourth of this figure The illness is prevented or greatly modified in the remainder and deaths from the disease are uncommon following vaccination

Passive Immunization

Passive immunization following exposure may be conferred by the intramuscular injection of the hyperimmune human or rabbit antiserum described above under immune therapy Serum should be admin

Myocarditis is a frequent complication which often results in sudden death when the patient gets up during convalescence, for this reason bed rest should be enforced for ten to fourteen days after the temperature has been normal, or longer if tachycardia, gallop rhythm, or other signs have been present No specific therapy is necessary, measures outlined under *Diphtheria* and in Chapter 10 should be followed

PREVENTION

In endemic or epidemic areas, the disease can be controlled best by attack on the flea vector, and secondarily on the rodent reservoir Extreme care should be taken in the isolation of animals inoculated with suspected plague material They should always be handled with rubber gloves since the infection can penetrate the unbroken skin as does tularemia

Droplet contamination of the air by patients with the pneumonic form should be prevented An aerosol of propylene or triethylene glycol in a concentration of one part to 100 000,000 of air sprayed constantly in the room masks on the patient and professional personnel and an oxygen tent for isolation may all be used Thorough scrubbing of utensils and of the room with a 1 1000 solution of bichloride of mercury is helpful in decontamination

Immunization

Regular prophylactic immunization with a vaccine containing 2000 million organisms per cc is of some value The initial subcutaneous dose should be 0 5 cc, followed in seven to ten days by a second injection of 1 cc, stimulating doses of 1 cc should be given every three to six months *At least seven days must elapse* after inoculation before any protective action is observed

Since the antiserum has some anti infective activity, intramuscular doses of 50 cc. may be used for passive immunization As the incubation period of the disease is only two days, serum would have to be given immediately after exposure, the effect is transient and the dose would have to be repeated if another exposure occurred within a week

Chemoprophylaxis

Sulfadiazine is apparently effective in the prevention of clinical disease The dose must be large, approaching that used for therapy Three grams daily given on a six hour schedule for seven days has been effective in preventing disease in known contacts Long continued administration at this dosage level may sensitize the patient to sulfonamides or lead to complications such as agranulocytosis, hemolysis and renal damage

Scarlet Fever

SUPPORTIVE THERAPY

Rest in bed is absolutely essential Because of the late appearance of some complications and the very high incidence of their occurrence in inadequately treated cases, it is advisable to keep patients with cases of average severity in bed for twelve days Patients with mild cases may be allowed up after eight days but should be followed carefully in the home thereafter

It is important to force the intake of fluids so that a urinary output of 1500 cc is assured A dilute urine of adequate volume is especially important if sulfonamides are administered

The diet should be composed entirely of

doses to all patients if streptomycin is not used It is cheap and has the additional advantage of being effective on oral administration In vitro no inhibition of the plague bacillus has been noted with concentrations of sulfadiazine as high as 0 2 Gm per 100 cc, even though the drug is effective in vivo

In relatively mild cases of the bubonic type an oral priming dose of 4–6 Gm should be followed by doses of 1–1 5 Gm every four hours until the temperature drops the dose should then be reduced to 0 5 Gm given on the same schedule for an additional ten to fifteen days A beneficial effect should be quickly noted, since the temperature in untreated cases usually remains high for only two to five days death will occur or recovery will have begun at the end of that time

In the primary septicemic and pneumonic types even larger doses seem to be necessary Up to 12 Gm may be required in the first day, and doses of 8–10 Gm daily until the temperature drops would not be excessive, a blood concentration of 15–20 mg per 100 cc should be maintained as a minimum Slightly smaller doses may be given if streptomycin is used concurrently but the blood concentration should not be allowed to drop below 10 mg

If the patient is comatose, a 5 per cent solution of sulfadiazine in water should be given intravenously The priming dose should be 0 1 Gm per kg body weight up to a maximum of 8 Gm subsequent doses can then be in the range of 3 Gm every six hours until the patient is able to take the drug by mouth

Immune Therapy

An immune serum has been prepared by the inoculation of live strains of organisms into horses or rabbits It acts chiefly by preventing invasion of tissue and hence, has little antitoxic power To be effective, serum therapy must be begun on the first or second day of illness, it is of value chiefly in the septicemic and pneumonic types

The dose has ranged from 20 to 160 cc, depending upon the potency of the serum and the severity of the infection, it should be repeated every six hours for three doses, and then once daily through the fifth day of illness Serum definitely seems to prolong life but whether it alters the mortality is still a moot point Serum should not be relied on alone but should be combined with streptomycin and sulfadiazine

Special Measures

The patient should be kept at absolute bed rest until the temperature has been normal for at least ten days Patients are often extremely restless, and morphine may be required for sedation

The bubos should not be incised during the acute phase, spread of the infection into the blood stream almost invariably follows Hot saline compresses should be used until it is certain that suppuration has occurred and incision should then be done with care while the patient is on chemotherapy Local injections of serum or chemotherapeutic agents have been of no value

Extremely toxemic patients show symptoms of peripheral circulatory collapse Saline and glucose infusions should be tried first, but plasma may be required to control the shock

The greatest caution should be exercised in isolation In the septicemic or pneumonic type mask, gown, gloves, and hood with plastic face piece should be used

Treatment of Complications

Secondary metastatic pneumonia due to the plague bacillus may require the use of oxygen as well as an increase in the dosage of chemotherapeutic agents In secondary pulmonary infection with ordinary pyogenic organisms, large doses of penicillin should be added to the sulfonamide or streptomycin

duces fewest reactions It contains 30–80 neutralizing (antitoxic antierythrogenic) units per cc A single dose of 2 cc per kg body weight not exceeding a total of 60 cc is injected intramuscularly better absorption is obtained if half is given in each buttock

If commercial antitoxin is used a single dose of 9000–18 000 units should be given intramuscularly in desperately ill patients the dose should be adjusted upward to 32 000 units Commercial antitoxin contains about 3500 units per cc It is rarely necessary to repeat the injection on the following day The administration of commercial *antitoxin which is prepared in horses is* almost invariably followed by serum sickness during convalescence

Convalescent serum gives almost as good results as commercial antitoxin It is preferable to administer it intravenously though it may be given intramuscularly if the quantity required is not too great In mild or moderately severe cases a dose of 60 cc is adequate in severe or septic cases as much as 100 to 300 cc may be required The average pooled convalescent serum contains 5 to 10 units per cc

If there is doubt as to the nature of the rash proof that it is caused by inadequate circulating antitoxin in the patient s blood can be obtained by the intradermal administration of 0 1 cc of antitoxin or convalescent serum The rash in the area surrounding the injection should fade for four to eight hours (Schultz Charlton reac*tion) This test is used for confirmation of* the diagnosis as well as for control of therapy

Special Measures

Because of the desquamation which occurs in convalescence rubbing alcohol should not be used on the skin The daily application of a light oil such as olive oil will prevent excessive drying and scaling and will lessen itching

The period of isolation is usually set by law however it is advisable to obtain two or three negative cultures on successive days before discontinuing isolation Isolation of discharges from the respiratory tract should be enforced to prevent infection in other members of the family In patients with scarlet fever due to streptococcic infection of an operative wound or burn it is important to observe unusual precautions such as the use of sterile sheets and gloves when dressings are being changed as well as oiling of the floor and blankets

Treatment of Complications

The majority of deaths result from complications rather than from the acute disease itself Even though chemotherapy has greatly reduced the incidence of complications (30–50 per cent in untreated cases) patients should still be carefully observed The most frequent complications were formerly sinusitis and rhinitis and the next most frequent was lymphadenitis Otitis is now the most frequent complication it may result from the overzealous use of throat irrigations or in children from the use of gargles and may be caused by a different organism from that producing the pharyngitis Mastoiditis occurs much less frequently since the introduction of chemotherapy

In septic cases the organism may invade the surrounding tissues by direct extension producing peritonsillar or retropharyngeal abscesses or it may metastasize to distant organs through invasion of the blood stream causing pneumonia meningitis arthritis or osteomyelitis

The appearance of complications may be an indication for combining sulfadiazine or antitoxin with penicillin therapy If the rash has already disappeared immune therapy is not likely to be helpful antitoxin merely neutralizes the erythrogenic exotoxin and has little effect on the strep-

liquids while the throat is sore, often ice cold fluids are tolerated better than warm ones When the membrane disappears soft foods can be added

An ice collar frequently replenished will often reduce the pain and swelling in the neck While the membrane is present throat irrigation with warm normal saline every two hours is often comforting and will decrease swelling Adults will find that a gargle of 250 cc of warm water in which two aspirin tablets (0 6 Gm) are dissolved often reduces local pain in the throat

SPECIFIC THERAPY

Chemotherapy

The drug of choice is penicillin For cases of average severity the intramuscular administration of 25 000 units of an aqueous solution of penicillin G every three hours day and night is adequate The dose for children is 10 000 units per Kg body weight per day When patients are treated in the home the injection of 90 000 to 150 000 units twice daily (or 300 000 units of procaine penicillin once daily) is more convenient for the physician If the case is of unusual severity or is septic in type, it would be wise to double this dosage

In mild cases penicillin should be administered for at least seven days though it is preferable to continue it for ten days in severe cases the drug should be given for twelve to fourteen days or more The streptococci disappear from the throat by the end of the second day of penicillin therapy The fever usually disappears by the fourth or fifth day and the need for hospitalization is usually slight after the eighth day

Though penicillin does not alter the rash its administration in adequate amounts definitely decreases the frequency of complications Relapses or reinfections which follow exposure to new contacts after the drug has been discontinued will usually respond to a second course

If penicillin is not available or if a prompt response has not been obtained from its use sulfadiazine should be administered The initial priming dose of 0 1 Gm per Kg body weight should not exceed a maximum of 5 Gm Subsequent doses in mild cases should be 1 Gm every four hours day and night until the temperature begins to drop (usually on the second day) the dose can then be cut in half and continued for five days more The maintenance dose in children is one sixth of the priming dose given on a four hour schedule In severe cases the maintenance dose should be 1 5 Gm every four hours for at least three days, it may be cut in half if the temperature has dropped significantly by that time, but should be continued for seven days more

The streptococci are not eradicated from the throat as rapidly or as completely by sulfadiazine as by penicillin Complications are reduced in number and severity but not to the extent that has been observed with penicillin

The *Streptococcus pyogenes* (which invariably falls in Group A by the Lancefield classification) is susceptible in vitro to 0 01 unit of penicillin per cc the dosage schedule outlined will probably achieve a blood concentration of 0 2 unit per cc The organism is usually susceptible to sulfadiazine in concentrations of 5 mg per 100 cc and the dose recommended will usually achieve blood levels of 15 mg per 100 cc Drug fastness develops more often to sulfonamides than to penicillin

Immune Therapy

The favorable results obtained with penicillin have relegated immune therapy to use in severe cases with marked toxemia septic cases with evidence of metastatic infection, or cases which have not responsed within four days to the administration of chemotherapy Human immune gamma globulin is the most available source of antitoxin and its injection pro-

cc of commercial antitoxin, 6–10 cc of gamma globulin or 10–20 cc of convalescent serum The value of this procedure for the average person after exposure is doubtful

Chemoprophylaxis

During an epidemic especially in an institution the implantation of streptococci can usually be prevented by the administration of a single daily dose of 0 5–1 0 Gm of sulfadiazine In the military services this dose has been employed for many weeks without an alarming number of reactions Long term prophylactic chemotherapy with sulfadiazine should not be administered unless careful medical or nursing supervision is available to detect reactions as soon as they appear Evidence of impending reaction can usually be detected within the first two weeks

In patients sensitive to sulfonamides effective prophylaxis can be achieved by oral administration of buffered penicillin though this method is much more expensive A daily dose of 200 000–1 000 000 units, depending on the size of the patient in equal divided doses one half hour before breakfast and supper will give serum levels in the range of 0 04 units per cc. Most strains of the organism are susceptible to 0 01 unit No toxic reactions have been noted even after months of administration Few penicillin fast strains arise

Septicemia (Pyogenic)

SEPTICEMIA should not be confused with bacteremia which is a much less serious condition or with bacterial endocarditis Septicemia usually occurs as a complication of some localized infection The most common sites of infection from which organisms enter the blood stream are the respiratory, gastrointestinal, and genitourinary tracts and the skin Transient bacteremia is often the initial phase of an invasion of the body by organisms which subsequently settle in their preferred site of growth It may also result when the pressure in a local site of infection is increased by accumulation of exudate or by manipulation causing organisms to spill over into the blood stream Acute bacterial endocarditis may be considered a form of septicemia but the duration of treatment should be prolonged to at least six weeks Follow up care should be based on the principles outlined for subacute bacterial endocarditis in Chapter 10 The subacute form of endocarditis progresses more slowly than the acute and the patient usually develops a considerable degree of immunity to the infecting organism this fact probably accounts for the frequent paucity of toxemic symptoms early in its course

SUPPORTIVE THERAPY

The most useful supportive measure is the frequent transfusion of fresh whole blood Direct transfusion is best but citrated blood is satisfactory If at all possible a donor convalescent from an infection with the same species of organism should be used Whether it is better to give 250–300 cc twice daily or 500 cc once daily must be decided on the basis of the patient's circulatory status If the myocardium has been damaged by infection large transfusions should be avoided Blood transfusions administered while the patient has fever are more likely to cause reactions than those given during an afebrile period It

tococci themselves Meningitis may necessitate the intrathecal administration of penicillin once or twice, daily Doses should not be administered which exceed 10 000 to 20 000 units in concentrations of 1000 units per cc If subacute bacterial endocarditis develops the dose of penicillin should be increased to around 1 000 000 units per day, in vitro susceptibility tests should be done on the organism recovered from the blood An abscess or osteomyelitis may have to be drained surgically

Though the complications discussed above increase in frequency as the clinical disease becomes more severe, toxic myocarditis and acute (hemorrhagic) glomerulonephritis may follow either mild or severe infections Myocarditis should be suspected if persistent tachycardia or a gallop rhythm is noted prolonged bed rest is essential in such cases Other measures are discussed under Diphtheria and in Chapter 10 If feasible, the urine should be examined daily for the presence of albumin and red blood cells If red cells are found and sulfadiazine is being used it should be discontinued Nephritis should be handled by the measures described in Chapter 18

TREATMENT OF CARRIERS

Though penicillin therapy quickly eradicates streptococci from the throat of patients during the acute phase of the disease, the same type of organism often returns or another type appears after a latent period of several weeks Reappearance of the original type is more common after sulfadiazine than after penicillin therapy

Sulfadiazine is more convenient to use for the eradication of organisms from the throat of a carrier an oral dose of 1 Gm twice daily for three days is usually sufficient Penicillin is less convenient, but more effective Twenty five thousand units of the aqueous solution given intramuscularly every three hours for four to seven days or 300 000 units of procaine penicillin injected once a day for the same length of time achieve equally good results Cultures should be taken two weeks after the end of therapy

PREVENTION

Nurses, house officers, and other personnel should receive a Dick test* for susceptibility to the exotoxin before being allowed to work on a contagious disease ward The test is performed by the intradermal injection of 0 1 cc of a standardized solution of toxin, if the area of reaction is 1 cm or greater at twenty four hours, the test is positive Usually a positive reaction indicates inadequate circulating antitoxin, in older children and adults it may indicate sensitivity to the body of the streptococcus or to the toxin

Regardless of their reaction to the Dick test, people who have had rheumatic fever should not be allowed to work on a ward where scarlet fever patients are housed

Active Immunization

In view of the efficacy of penicillin therapy, the necessity for immunization of children with positive Dick tests has recently been questioned In any event, prophylactic immunization will only prevent the rash it will not prevent the sore throat or sepsis Should prophylaxis seem advisable, the standardized toxin can be injected subcutaneously at weekly intervals in doses of 500 2000, 8000, 25 000, and 80 000 units respectively For large individuals these doses can be increased by half A repeat Dick test should be done at the end of six months

Passive Immunization

Passive immunization can be temporarily conferred on debilitated patients or on those recovering from some other disease by the intramuscular administration of 3

* See Chapter 48

rhoeae, or *Fusobacterium plautivincenti* (fusospirochetes) the dose should be 50,000 units every two hours day and night This amount will usually achieve a blood concentration of 1 5–2 0 units per cc of blood within fifteen to thirty minutes after an injection After the blood cultures have become negative and the temperature has been normal for two days, procaine penicillin in doses of 300 000 units every twelve hours may be administered for another five to seven days

Septicemia due to less susceptible organisms, such as *Micrococcus pyogenes (Staphylococcus aureus)* *Streptococcus mitis* (*Str viridans*) *Neisseria intracellularis* (meningococcus) *Clostridium tetani* and *Cl welchii*, *Bacillus anthracis*, *Actinomyces bovis*, *Spirillum minus*, *Borrelia novyi*, and *Streptobacillus moniliformis* should be treated with 100 000–200 000 units of penicillin every two hours In infections due to these organisms it may be wise to combine streptomycin or sulfadiazine with penicillin therapy during the acute febrile phase After the infection is under control procaine penicillin in doses of 500 000–600 000 units may be given twice daily for an additional week

In infections with organisms which are relatively nonsusceptible (resistant) to the action of penicillin, such as some strains of *Str mitis*, *Str faecalis* *Str anaerobius*, and *Leptospira icterohaemorrhagiae*, the dose of penicillin should be 300 000–1 000 000 units every two hours A few strains of gram negative bacilli will also be inhibited by this amount This dosage schedule should achieve a blood concentration of 7–15 units per cc but often the level obtained is considerably below that which is expected In fecal streptococcal infections the simultaneous intramuscular administration of 2 4 Gm of streptomycin daily exerts a synergistic effect

If the desired blood concentration of penicillin is not attained with a large dose every two hours, the oral administration of 'benemid in a dose of 0 5 Gm every four to six hours usually will produce a four to eight fold increase in the penicillin level within twelve hours Mild toxic symptoms, such as nausea, occasionally occur and rarely a skin rash is produced The drug is useful for a short period of administration in young patients who have no renal lesions, since it blocks the excretion of the antibiotic and other substances by kidney tubules In older individuals, massive doses of penicillin (up to 20,000 000 units daily) may be safer

The intramuscular administration of streptomycin (or dihydrostreptomycin) is preferable in infections with most gram negative bacilli and some gram positive and gram negative cocci which are penicillin fast The drug should be given in doses of 1 Gm every four to six hours if the culture shows such organisms as *Escherichia coli* *Klebsiella pneumoniae* (Friedlander's bacillus), *Brucella sp*, *Hemophilus sp*, *Shigella dysenteriae*, *Aerobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pasteurella tularensis*, or *Past pestis* Blood levels of 20–40 μg per cc are achieved, but this dose will frequently produce toxic symptoms in the eighth cranial nerve and should not be given for longer than ten to fourteen days When the temperature has been normal for two days, the dose should be cut in half but continued for a total of ten days If the organisms have not disappeared at the end of one week, it is probable that they have become streptomycin fast, and other antibiotic therapy should be substituted Drug fastness develops more frequently with streptomycin therapy than with other chemotherapeutic agents

When certain species of penicillin fast organisms, such as *Pasteurella pestis* or *Brucella sp* are responsible for the septicemia or when other streptomycin susceptible organisms are present in large numbers streptomycin should be combined with

may therefore, be wise to allow twenty four to thirty six hours of chemotherapy before starting transfusions, and to give them in the morning with the patient and donor fasting

SPECIFIC THERAPY

Chemotherapy

Certain types of septicemias such as that due to *Escherichia coli* entering from the urinary tract in elderly individuals or that occurring in children with osteomyelitis caused by *Micrococcus pyogenes* (hemolytic *Staphylococcus aureus*) progress with great speed It is important therefore, that therapy be instituted rapidly or death may ensue Also, irreparable damage to the heart kidneys or other organs may occur Repeated blood cultures should be taken at intervals of two to four hours so that a positive identification of the etiologic agent can be made Therapy may be started on the basis of the clinical picture, but the bacteriologic studies are necessary to serve as a check on the selection of the chemo therapeutic agent

Blood cultures planted by the pour plate technic also give an estimate of the number of invading bacteria and hence govern to some extent the dose of the drug selected The doses listed below are for septicemias with 10 to 20 colonies per cc of blood for heavier invasions the dose should be in creased and at least two different chemo therapeutic agents administered Certain combinations of drugs are synergistic since they seem to affect different enzyme systems of bacteria Other combinations are an tagonistic and small doses of one antibiotic may block the therapeutic action of large doses of another The in vitro susceptibility of the etiologic agent should be assayed since the dose is governed by this factor If possible the *bactericidal* concentration at which the organism is killed should be determined as well as the *bacteriostatic* level at which the bacterium is merely in hibited in its growth Penicillin and strep tomycin are the two chemotherapeutic agents available for parenteral use at this writing which can safely be given in doses which may achieve both bacteriostatic and bactericidal action It is almost imperative that the blood concentrations of the chemo-therapeutic agents exceed twice the level necessary to inhibit the organism completely in vitro In order to facilitate penetration into a locally infected area it is much better, if possible to achieve a blood concentration of the drug five to ten times greater than the organism s in vitro level of suscepti bility Blood concentrations of the chemo-therapeutic agents should be determined thirty minutes to one hour after a dose

The fluctuating blood level which is attained by the administration of a chemo-therapeutic agent two or three times daily is satisfactory for severe localized infections in septicemia however the blood concen tration of the drug should be raised rapidly to the optimum level and maintained there as steadily as possible It is probably wise always to start with an intravenous priming dose even though subsequent doses may be given orally In some instances a con tinuous intravenous or intramuscular drip is preferable to periodic oral subcutaneous, or intramuscular administration It is essen tial that absorption of the drugs be com plete and rapid hence slowly mobilized preparations such as procaine penicillin or penicillin in oil and wax should not be used until the patient is afebrile and the cultures have been negative for several days

When the clinical picture suggests infec tion with a penicillin susceptible organism or if such an organism has already been recovered from a localized infection injec tions of an aqueous solution of crystalline penicillin G should be started

If the organism is a highly susceptible one such as *Diplococcus pneumoniae*, *Streptococcus hemolyticus*, *Neisseria gonor*

explains the relapse often seen when therapy with these drugs is discontinued after an apparent arrest of the infection has been obtained They probably should not be relied on alone in severe septicemias Chloramphenicol blocks the bactericidal action of even high concentrations of penicillin and these two drugs should not be used together Interference or antagonism with the therapeutic action of penicillin is also exerted by aureomycin and terramycin but the range of concentration of the drugs in which the effect is noted is narrower The use of multiple dose schedules may eventually allow the simultaneous administration of large doses of the drugs without antagonism but to date no synergistic effect has been noted in such schedules Streptomycin does not interfere with the action of penicillin and its administration may under certain conditions break through the antagonism of chloramphenicol with penicillin and restore the bacteriostatic effect of the latter drug

Further discussion concerning combined chemotherapy of the septicemic form of certain specific diseases is to be found in the sections on anthrax brucellosis plague and other conditions

Immune Therapy

The use of specific immune sera and antitoxin to increase rapidly the number of immune bodies in the blood has been discussed in the sections on individual diseases

Special Measures

Any lesion which is freeing organisms into the blood stream should be corrected surgically if feasible

Complications

Metastatic abscesses may occur in the lungs kidneys joints pericardium brain skin or other organs Myocarditis nephritis arthritis and similar conditions may appear as late manifestations after the acute symptoms have subsided

PREVENTION

Chemoprophylaxis before surgical procedures should follow the principles outlined in Chapter 42 and under Scarlet Fever in this chapter

Septic Sore Throat

MOST cases of septic sore throat are caused by infection with *Streptococcus pyogenes* (beta hemolytic streptococcus) the next most common causative organism is *Micrococcus pyogenes* (hemolytic staphylococcus aureus) Both supportive and specific therapy should follow the general principles discussed under Scarlet Fever Antitoxin or convalescent serum is of little value

PREVENTION

Ultraviolet lights or vapors of triethylene or propylene glycol may be useful under rigidly controlled conditions for control of cross infection

Prophylactic chemotherapy should be given by the same regimen employed for the prevention of scarlet fever

Active or passive immunization is useless

sulfadiazine, aureomycin, terramycin, or chloramphenicol As experience with newer antibiotics accumulates, streptomycin may be used less and less

The use of streptomycin in miliary tuberculosis with positive blood cultures is discussed in Chapter 16

A sulfonamide should be used in conjunction with antibiotic therapy when septicemia is caused by organisms which are relatively insensitive to penicillin and streptomycin it should not be used alone unless the patient is allergic to all antibiotics Sulfadiazine, in spite of its tendency to precipitate in the renal tubules, is the best all round member of this group of drugs The initial dose should be 0 1 Gm per Kg body weight (maximum 5 Gm) and should be given by the intravenous route The maintenance intravenous dose is half this amount given at six hour intervals For intravenous administration the drug should be made up as a 5 per cent solution of the sodium salt in distilled water or isotonic sodium chloride If at all feasible, it is best to give the maintenance dose orally, 1 Gm every four hours day and night It is wise to keep the blood concentration below 15 mg per 100 cc except in unusual circumstances such as infection with plague If the fluid intake is sufficient to produce a daily urinary output of 1500 cc or more, it is not necessary to alkalinize the urine by the administration of sodium bicarbonate or other forms of base Preparations containing two or more sulfonamides have no therapeutic advantage over sulfadiazine alone

Aureomycin should be used for infections with gram negative or gram positive cocci or bacilli which are penicillin and streptomycin fast In some infections such as acute brucellosis the drug appears to be the one of choice Infections due to *Proteus sp* and *Pseudomonas sp* have not been affected Aureomycin should be given orally The priming dose is 10–20 mg per Kg body weight the maintenance dose should be 50–100 mg per Kg per day The drug is equally effective whether given on a two, three, four, or six hour schedule If the amount administered at one time is kept small and is given with food and the interval between doses is decreased, nausea is lessened Occasionally the administration of an antihistaminic, an antispasmodic, and a sedative will abolish nausea At the present time, in spite of careful buffering intravenous administration of the drug produces many local reactions, such as pain and thrombosis at the site of injection The intravenous route must be used if nausea persists however The intravenous dose is 5 mg per Kg body weight every eight hours

The use of aureomycin in rickettsial and viral diseases is discussed in other chapters

Chloramphenicol is also effective in some bacterial infections which are penicillin and streptomycin fast but it does not have as wide a chemotherapeutic spectrum as does aureomycin It is the drug of choice in septicemias due to *Salmonella sp*, however The drug is relatively ineffective in infections due to *Proteus sp* but occasional strains will respond It is given orally in a daily dose of 0 1 Gm per Kg body weight, on a four or six hour schedule Adequate experience with the parenteral use of the drug in bacterial infections is not recorded at present

The use of chloramphenicol in rickettsial and certain viral infections which are septicemias at some stage of the disease is discussed in other chapters

Terramycin in doses of 50 to 100 mg per Kg body weight daily on a six hour schedule also may be helpful in some infections As a general rule organisms resistant to aureomycin will not respond to terramycin

Aureomycin chloramphenicol and terramycin are bacteriostatic and rarely achieve a bactericidal effect This fact probably

treatment emphasizes the extreme importance of prophylactic immunization

Treatment must be highly individualized, regarding immune therapy, sedation, surgical measures, and chemotherapy

Chemotherapy

Intramuscular doses of 50,000–100,000 units of an aqueous solution of penicillin should be given every three hours until clinical recovery has begun Penicillin has no effect on the toxin or on the spores of *Clostridium tetani* it is bacteriostatic in a concentration of 0 1 units per cc. against the bacillary form of the organism, and hence may reduce slightly the amount of toxin being formed by the growing organisms Penicillin is particularly useful in controlling pyogenic infection of the wound (*pus lowers the oxygen content of* tissue and favors the formation of toxin) and in preventing the development of pneumonia and parotitis— two severe complications which frequently lead to death

If the wound is very severely contaminated or if the patient has an idiosyncrasy to penicillin, the daily intravenous injection of 5 Gm of sulfadiazine may be of some value

Some of the newer antibiotics, such as chloramphenicol, are effective in high dilution against tetanus bacilli in vitro but no data are available on clinical results

Special Measures

Sedation After antitoxin has been injected the most important phase in the care of patients with tetanus is sedation Death may result from asphyxia caused by spasm of the muscles of respiration from aspiration pneumonia or from exhaustion caused by convulsions The patient must be placed in an absolutely quiet darkened room and protected from any stimulation even that resulting from such minor disturbances as noises drafts or unnecessary handling of the bedclothes It is highly desirable to have *special nurses and, if possible*, ones who have nursed previous cases of tetanus Immediate preparations should be made in the patient s room for emer*gency tracheotomy with establishment and* maintenance of an adequate airway should respiratory spasm suddenly occur * A mechanical suction device with rubber tipped catheters for aspiration of mucus and vomitus should be kept constantly by the bed

In the hospital, tribromoethanol ('Avertin with amylene hydrate") is probably the most useful sedative Each dose must be freshly prepared and the *p*H tested with congo red indicator before use A rectal tube should be inserted and left in place for the first several days, so that the medication can be given with the least disturbance *to the patient* The initial dose in cases of average severity should be in the range of 10–25 mg per Kg body weight The dose may have to be increased to 40–50 mg per Kg when convulsions are present, but for cases of average severity subsequent doses of 10–15 mg per Kg at intervals of fifteen to sixty minutes are satisfactory The frequency and size of subsequent doses should be determined by the rigidity of muscles, such as those of the abdominal wall

Sodium amytal is a more satisfactory drug for use in the home The intramuscular injection of 5 mg per Kg body weight as a 10 per cent aqueous solution is satisfactory for most cases, the total dose given in a single injection should not exceed 0 4 Gm for children and 0 8 Gm for adults The same dosage may be used intravenously for severely ill patients especially where asphyxial spasm is occurring since the effect is more rapid When it is given intravenously, the rate of flow should be accurately timed at 1 cc per minute For mild cases the drug may be given orally or administered rectally

* See Chapter 37

Tetanus

SUPPORTIVE THERAPY

Supportive therapy should be administered with great care in order to avoid complications Fluid need not be forced beyond the point necessary to prevent dehydration (the patient often sweats profusely) The diet should be composed entirely of liquids at first If the patient has no difficulty in swallowing or coughing after he is under the influence of sedatives fluids may be administered cautiously by mouth and soft foods may be added when he can make slight chewing movements Occasionally a nasal tube may be used in patients who cannot swallow but there is a definite risk that aspiration pneumonia and lung abscess may result from the vomiting of tube feedings In severely ill patients it is safer to resort to feeding by continuous intravenous drip

In order to reduce the hazard of aspiration of saliva mucus or regurgitated food the head should not be elevated After the patient has received a dose of sedative he should be gently turned on one side to aerate the lungs and drain any material in the bronchi from the mouth after the next dose he should be turned to the opposite side Care to the mouth should be given to prevent parotitis only after a dose of sedative

SPECIFIC THERAPY

Immune Therapy

The immediate administration of a full dose of antitoxin is imperative as soon as a diagnosis of tetanus is made The patient should be sedated before the injection is made The toxin must be neutralized in the wound or in the blood before it reaches the central nervous system hence an adequate circulating level of antitoxin must be quickly achieved After a preliminary skin test (during the fifteen minute wait the serum should be warmed to body temperature) 40 000 units should be given intravenously and 60 000 units intramuscularly It is wise to inject the intramuscular dose into two or three separate sites such as the anterolateral aspect of both thighs and the deltoid muscle of one arm so as to ensure rapid absorption If the wound can be located and is accessible 20 000 units may be injected locally around it

In mild or moderately severe cases only a single dose may be necessary Many authors feel that 30 000 units of antitoxin in children and 80 000 units in adults constitute adequate total dosage others do not agree In severe cases it is probably wise to give an additional 40 000 units intramuscularly at twelve-hour intervals until a total dose of 200 000 units has been given in the first twenty four to thirty-six hours 5,000 units should be given each succeeding day until recovery begins

No antitoxin should be given intrathecally the edema produced by the antigen antibody reaction is apt to cause death

The greatest single factor affecting the case fatality rate in nonimmunized persons is the interval elapsing between the time of the wound and the appearance of symptoms Even in adequately treated cases with an incubation period of less than six days the mortality for all age groups is 75–80 per cent With an incubation period longer than six days the mortality is reduced to 20–25 per cent In general the prognosis is better in older children than in any other age group and is poorest in adults The type and location of the wound also affect the prognosis The presence of fever is a poor prognostic sign The relatively high mortality in spite of the best available

similar surgical condition which is not infected with tetanus bacilli Small puncture or penetrating wounds which have healed should be left undisturbed No surgery of any kind should be undertaken until after the patient has had a full dose of antitoxin and adequate sedation If pus is present the wound may be incised but should be left open it may be irrigated with an oxidizing agent such as warm potassium permanganate solution or packed with zinc peroxide ointment If the presence of a foreign body is suspected the wound should be explored and any devitalized tissue debrided This is especially important if the wound has been caused by a shotgun blast at close range where wadding or clothing may be forced into tissue

Treatment of Complications

Pneumonia is the most serious complication If penicillin is not being given it should be instituted as soon as this complication develops in the doses outlined above Lung abscess may require surgical intervention later Parotitis should be treated with penicillin Compression fractures occasionally result from the severe convulsions they should be treated with a cast in the usual fashion after the convulsions are controlled

PREVENTION

Active Immunization

The difficulties in treating tetanus can be largely avoided by active immunization of all children Alum precipitated toxoid originally containing 15 000 minimum lethal doses per cc should be given in an intramuscular injection of 0 5–1 0 cc depending on the size of the individual the injection should be repeated after an interval of three weeks to three months If fluid toxoid is used three injections of 1 0 cc. should be given at three- to six week intervals These schedules will induce antitoxin levels greater than 1 unit per cc of blood three months after injection By six months the levels are dropping but are still adequate to prevent clinical disease

As soon as an injury is sustained a booster injection of toxoid should be given In adults who have been immunized within four to six years previously an injection of 0 5–1 0 cc will raise the antitoxin titer to 2 units per cc. within five days in children the intradermal injection of at least 0 1 cc or the subcutaneous injection of 0 5 cc will achieve the same result

Passive Immunization

Since the average incubation period of tetanus is about seven or eight days more than enough time is usually available after an injury to produce passive immunization In children the intramuscular injection of 1500 units of antitoxin will achieve residual blood levels of 0 1–0 25 units per cc after one week in adults a dose of 3000 units is satisfactory If the wound is small and the chance of contamination slight this dose is adequate If the wound has occurred in farming country or around wharves or riding stables in cities or is grossly contaminated with foreign material a prophylactic injection of 10 000 units is much safer

If there is reasonable suspicion that the wound may have been contaminated with tetanus spores antitoxin should be given even to individuals who have recently received active immunization and a booster dose of toxoid

The intramuscular injection of 0 2–0.4 Gm of sodium phenobarbital or the rectal administration of 30–60 cc of paraldehyde in oil is satisfactory for mild cases

When the patient is under constant supervision and the physician has had experience in the use of mephenesin tubocurarine or β erythroidine these drugs may be used as they have limited use in cases with severe muscle spasm or convulsions Mephenesin (myanesin tolserol) is a synthetic compound which has a curare-like action The oral form of the drug (tolserol) has been used increasingly in tetanus For adults a dose of 1 Gm every two hours should be started but may have to be increased to as much as 3 5 Gm Phenobarbital in doses sufficient to produce light sleep (32–130 mg) should be given concurrently two to three times daily Convulsions in mild cases are controlled by the second or third day The intravenous form of the drug (myanesin) has been used in doses of 1 Gm, as a 2 per cent solution in water, two to three times a day Hemoglobinuria has been reported following intravenous use

Tubocurarine may be administered intravenously or intramuscularly in a dose of 1 unit (0 15 mg of the active principle) per kg an injection is usually effective for only fifteen minutes to an hour and repeated doses have a cumulative effect The drug should be given very slowly over a period of at least fifteen minutes the intravenous route is the safest The rate of injection and the interval between doses should be regulated by the patient s clinical response which lags about three minutes behind the injection A preparation of the active principle containing 27 mg of d tubocurarine (which is equivalent to 180 units of curare) in a cubic centimeter of a 4 8 per cent solution of peanut oil is effective for eighteen to twenty four hours and may be cumulative The initial intramuscular dose of 3 5 units per kg body weight (not to exceed a total of 2 cc) exerts a relaxing effect within one to three hours Subsequent doses are required at intervals of eighteen to twenty four hours the daily maintenance dose is in the range of 0 6–2 0 cc and must be regulated by the clinical response Curare is a dangerous drug in inexperienced hands however and its action is often unpredictable

β Erythroidine may be given orally in a dose of 20 mg per hour the dose may be increased as needed for the individual case to a maximum of 100 mg per hour Three hundred milligrams is about equivalent to 50 mg of curare

With any type of sedation the respiratory exchange must be carefully observed to avoid cyanosis or blockage from overdosage respiratory stimuli are depressed by avertin and barbiturates while the muscle contractions are blocked locally by the curare group of drugs Neostigmine is the antidote for curare and mephenesin the methylsulfate is administered intravenously in a dose of 0 5 mg (1 cc of 1 2000 dilution)

Relaxation of Sphincters Because of the spasm of the sphincters the patient may have urinary retention and constipation An attempt should be made to establish an automatic bladder Catheterization should be resorted to only after other measures have failed Furmethide iodide should be given three or four times daily in an oral dose of 5–10 mg or a subcutaneous dose of 3–7 mg Occasionally painful contraction of bladder muscles may be induced without micturition In such cases the intramuscular injection of 0 5 mg of ergotamine tartrate is said to relax the sphincter tonus and allow voiding Constipation will do no great harm after muscle spasticity has been controlled by sedation and digital examination has ruled out the presence of fecal impaction enemas may be given

Surgical Treatment The site of infection should be treated exactly like any

suppurating nodes usually does not shorten the course or improve the result

An ophthalmic solution of aureomycin containing 25 mg in 5 cc of water, may be helpful in the ocular form but should not be relied on alone Two to three drops are instilled in each conjunctiva every three hours for ten to fourteen days

Rubber glove isolation technic should be used

Treatment of Complications

Tularemic meningitis occasionally occurs, it may require intrathecal as well as parenteral administration of streptomycin Nephritis rarely occurs during convalescence and should be treated as described in Chapter 18 on kidney disease

TREATMENT OF CARRIERS

No carriers are reported

PREVENTION

An oxidized vaccine of uniform turbidity has been prepared Initial immunization is obtained by three doses of 0 5 cc each injected subcutaneously in alternate arms on successive days Yearly revaccination is required, the first injection should not exceed 0 25 cc and the second and third doses should be governed by the degree of local reaction obtained

Rubber gloves should be used when animals are handled

No data are available on the effectiveness of preventive chemotherapy or immunotherapy

Typhoid Fever

SUPPORTIVE THERAPY

Diet and good nursing care are of extreme importance The diet should contain between 3000 and 4000 calories depending on the height of the temperature, and should be low in residue in order to prevent irritation of ulcerated Peyer s patches Fluid intake should be great enough to insure a urinary output of 1500 cc usually 3000 cc of fluids daily is adequate

SPECIFIC THERAPY

Chemotherapy

The drug of choice at present is chloramphenicol An oral priming dose of 50 mg per Kg body weight is followed by a dose of 0 25 Gm orally every two hours until the temperature has reached normal (usually within four days) Blood levels in the range of 20 μg per cc are achieved with this dose The drug should be continued in a dosage of 0 25 Gm every four hours for at least the next five days if it is continued for three weeks the chance of relapse is slight Relapses have occurred after afebrile periods of ten to sixteen days in patients treated for eight days or less but have responded in three days to a second course of the drug

An alternative schedule which requires less nursing time and which seems to be equally as effective in the patients treated thus far, consists of an initial oral dose of 3–4 G, followed by 1 5 Gm every twelve hours until the temperature becomes normal A single oral dose of 1 5 Gm is given for the next seven days when the dose is reduced to 1 Gm through the fourteenth day of therapy

Organisms disappear from the blood in two to six hours If stool cultures are still negative as they will be in cases seen within the first week of the disease they usually remain negative during treatment if cultures are already positive they become negative in two to four days The appearance of organisms in stools or urine after therapy is discontinued often precedes

Tularemia

SUPPORTIVE THERAPY

Local application of ice bags or aspiration of necrotic material often reduces the pain of the buboes

SPECIFIC THERAPY

Chemotherapy

Streptomycin (or dihydrostreptomycin) is extremely effective in all types of the disease In the ulceroglandular and oculoglandular types with or without pleuropulmonary involvement it should be given intramuscularly every four hours in doses ranging from 0 1–0 3 Gm This dose will achieve a blood level of at least 6 μg per cc The temperature usually begins to drop on the second or third day the total daily dose should not be changed but the interval between injections may then be increased to eight hours In the ulceroglandular type the drug should be administered for six days in cases of pleuropulmonary involvement administration should be continued at least seven days

In the typhoid type which has a mortality three times that of the glandular types the dose should be at least 3 Gm daily and should be continued for at least seven days after the temperature is normal

Aureomycin has been used in oral doses of 0 5 Gm every four hours for three to four days When the temperature subsides the interval between doses may be increased to six hours but the drug should be continued for an additional five days Chloramphenicol has not been as effective as aureomycin in a limited trial

p Aminobenzoic acid (PABA) in large doses will have some effect if antibiotics are not available or are contraindicated

Effective chemotherapy may induce a Herxheimer like reaction with a sudden elevation in temperature after it has begun to fall A high degree of allergy develops quickly in the disease and the destruction of large numbers of organisms releases a huge amount of antigen The massive release of antigen may also temporarily depress the serum agglutinin titer until the antigen is all neutralized

The concentration of streptomycin required for bacteriostasis of *Pasteurella tularensis* in vitro is 0 3 μg per cc a level of 6 μg per cc will kill the organisms in one minute Aureomycin in a concentration of 0 5 μg per cc completely inhibits the organisms for twenty four hours Drug fastness rarely develops to either antibiotic within the short period of therapy necessary to control the infection

Immune Therapy

Immune horse serum is commercially available goat serum can be obtained for patients who are allergic to horse serum Serum therapy is usually ineffective after the fourth week of the disease Before that time the dosage is 30 cc given intramuscularly every day for three days If pneumonia is present the initial dose should be 60 cc 30 cc should then be given each successive day until a clinical response is obtained

Antiserum is necessary only in extremely toxemic patients such as those with the typhoid type or with meningitis, it should always be combined with chemotherapy

Special Measures

If treatment is begun after the tenth [illegible]

enlarged lymph nodes Suppurating nodes should be drained surgically and chemotherapy should be continued until the incision is healed The injection of chemotherapeutic agents or immune serum into

teriostatic action of the drugs Perforation requires immediate surgical repair Hemorrhage should be treated by the regimen employed for bleeding peptic ulcer * *Thrombophlebitis hypostatic pneumonia* and furuncles of the skin are common complications the treatment of these conditions is discussed in other chapters Suppuration of intra abdominal lymph nodes with secondary bacterial infection may require surgical drainage

Special Measures

All excreta and linen should be isolated *until sterilized*

Chloramphenicol and aureomycin suppress the growth of *Salmonella* in stool and urine cultures In 2–3 per cent of untreated patients the carrier state is detected in convalescence by culture of the stools at monthly intervals after the disease has subsided Information on cultures of stools made after this time from patients treated with these antibiotics is scanty For protection of others stools and urine should be cultured at least once monthly for eight months after recovery or two cultures of bile should be made one week apart in the sixth month of convalescence after duodenal intubation with the instillation of sterile magnesium sulfate

* See Chapter 17

TREATMENT OF CARRIERS

No chemotherapeutic agent—not even those which are effective in the treatment of the acute disease—has permanently eradicated organisms from the stools of carriers the bacilli localize in the gallbladder Chloramphenicol is found in the bile in concentrations half that of the blood Aureomycin has not been found in bile recovered from biliary drainage The oral administration of gallbladder dyes which contain iodine occasionally will suppress the organisms temporarily Surgical removal of the gallbladder is usually necessary *to eradicate the carrier state*

PREVENTION

Effective vaccines are made from cultures of *S typhosa* a vaccine which also contains *S paratyphi* and *S schottmuelleri* (paratyphoid types A and B) is known as triple vaccine On the initial immunization a vaccine containing at least 100 000 000 organisms of each type per cc should be given subcutaneously in doses of 0.5 1.0 and 1.0 cc at weekly intervals After an initial subcutaneous immunization yearly boosters of 0.5 cc subcutaneously or 0.1 cc intradermally are usually adequate

No information is available on the effectiveness of chemotherapy or immunotherapy *in prevention*

Yaws

SPECIFIC THERAPY

Chemotherapy

The drug of choice for the treatment of any stage of yaws is penicillin The therapy of an accidental extragenital infection in a single individual should be designed to cure the disease completely A decidedly different problem is presented by *the mass treatment* of large groups of natives as a public health measure the aim *in that case* is simply to abolish infectivity by sterilization of the mucocutaneous lesions

In primary and secondary yaws penicillin is extremely effective in an intramuscular dose of 15 000 units of the aqueous solution every three hours day and night Usually a Herxheimer like febrile reaction will occur from two to eight hours after the

a recrudescence or clinical relapse (See also special measures and treatment of carriers) The titer of agglutinins in the blood (Widal test) may not reach as high levels after chemotherapy as might be expected in untreated patients

Aureomycin is relatively ineffective in typhoid fever Cases have shown clinical improvement to 0 5 Gm given orally every two to three hours but the response is not as good as after chloramphenicol

Chemotherapy should be started immediately when the patient is first seen regardless of the duration of the disease Chloramphenicol is known to penetrate cells and to be effective against the intracellular phase of rickettsias and of some viruses, its efficacy in typhoid fever after the second week of symptoms must be due in some measure to this characteristic

Other chemotherapeutic agents available at present are of limited value in typhoid fever Streptomycin given orally or intramuscularly in doses as high as 4 Gm daily was originally reported to be effective subsequent experience has not borne out this report Better results have been obtained with a combination of penicillin (400 000 units every two hours intramuscularly) with sulfathiazole (1 5 Gm every four hours orally) It is possible that these drugs by reducing the number of normal bowel flora may be of some use if chloramphenicol is not available certainly they will reduce the severity of peritonitis should perforation occur

The suggested doses of any of the drugs mentioned will give blood levels of the chemotherapeutic agent which are bacteriostatic against strains of *Salmonella typhosa* in vitro Incomplete inhibition of growth is obtained with chloramphenicol in concentrations as small as 0 25 μg per cc. but 1000 μg is not bactericidal Complete inhibition is obtained with aureomycin at 6–25 μg per cc., with penicillin and sulfathiazole at 1 unit per cc. and 10 mg per 100 cc, respectively and with streptomycin at 9–18 μg per cc

Immune Therapy

An effective immune antiserum has been prepared in horses It is not available commercially in the United States but may be available in countries of the British Commonwealth The serum is effective against organisms having the Vi antigen which is found only in virulent strains and against the O antigen, which is a component of the bacterial body and probably includes the endotoxin The serum appears to reduce the clinical severity of the illness to decrease the toxemia of the patient and to shorten the course of the disease It aids in clearing the blood stream, but should not affect intracellular organisms it is therefore ineffective if given after the third week of the disease

In a case of ordinary severity, 33 cc (one ampule) is given intramuscularly every day for three days in hyperacute infections 66 cc is given as the initial dose The serum should be combined with chemotherapy Convalescent serum is much less effective

Where laboratory facilities permit a type specific bacteriophage may be made and administered intravenously in a single dose of 1 cc diluted in 500 cc of 5 per cent dextrose This technic would be useful in the therapy of atypical strains which appear unpredictably

Treatment of Complications

Optimum treatment, including adequate chemotherapy does not prevent the later development of complications Hemorrhage from an ulcerated Peyer s patch and perforation with peritonitis are the most dangerous complications They usually occur during the third and fourth weeks of the disease The symptoms of perforation may be quite atypical in patients who have received antibiotic therapy and the signs of peritonitis may be obscured by the bac

In the absence of supplies of more effective drugs and of personnel trained to give intravenous injections intramuscular injections of bismuth subsalicylate (or the soluble bismuth sodium tartrate) 0 2 Gm, should be given twice weekly as long as the patient can be kept under observation

Special Measures

Usually the cutaneous ulcers are secondarily infected Hot saline compresses or dressings wet with Dakin s solution will reduce bacterial contamination and improve the appearance and odor of local lesions On occasion debridement of some areas is necessary

The serologic test for syphilis should be checked twice yearly for an indefinite period If at all feasible, fluoroscopic studies of the aorta and examination of the cerebrospinal fluid should be carried out at yearly intervals

Treatment of Complications

Aortitis and lesions of the bones or central nervous system should be treated by the schedules outlined in Chapter 39

initial injection but will subside within twelve to eighteen hours The lesions become darkfield negative in twelve to sixteen hours, joint pains disappear within one to two days and the extremely painful crab lesions on the soles of the feet disappear in two to three days The open lesions of the skin and mucous membranes heal within three weeks

Treatment with penicillin (500 000 units total) for as short a time as six days will eradicate infectivity for a period of months a larger dose—40 000 units every three hours for four days (1 2 million units total)—is no more effective than the smaller one A twelve day period of treatment with the smaller dose (1 5 million units total) is apparently more effective in inducing a remission and prolonging the period of sterilization of the lesions It is likely that best long term results will be obtained by the same doses used for early syphilis—50 000 units every two hours for eight days (4 800 000 units total)

The serologic test for syphilis reverts less promptly and less completely in yaws than in syphilis treated with similar doses of penicillin

As in the case of syphilis which yaws mimics in many respects late tertiary lesions may develop Few data are available on the treatment of this stage The schedules discussed in Chapter 39 should be used a minimum of 90 000 units daily (3 5 million total) should be given

A single daily injection of 300 000 units of procaine penicillin (twenty four hour duration) or biweekly injection of 600 000 units of the variety with aluminum monostearate for more prolonged action would be more convenient in the treatment of large numbers of cases One injection of 300 000 units given to each clinically active case when the diagnosis was made has been effective as a stopgap public health measure in reducing the spread of the infection to new cases Three injections at forty eight-hour intervals in primary and secondary yaws has effected healing of lesions in ten to fifteen days Cases of less than six months duration have remained clinically and serologically negative after a year cases of longer duration have not always attained negative sera More detailed data over a longer period of time are necessary to evaluate such schedules in individual patients

In the absence of supplies of penicillin arsenic should be used Three weekly intravenous injections of neoarsphenamine, 0 6 Gm will sterilize the local lesions of primary and secondary yaws and induce a temporary remission if six weekly injections are given the relapse rate at twenty four months is reduced to roughly 13 per cent A better schedule for the treatment of an individual patient would be to give eight doses of mapharsen (0 06 Gm) intravenously at weekly intervals the first four doses should be accompanied by intramuscular injections of 0 2 Gm of bismuth subsalicylate in oil and the last should be followed by eight weekly injections of bismuth

In the mass treatment of natives in tropical areas an oral preparation would be most desirable Acetarsone (stovarsol) a pentavalent arsenical has been used orally in daily doses starting with 1 Gm the dose is increased by 1 Gm each day until the third day and the dose of 3 Gm is continued until a total of 8 to 15 Gm has been given This dosage apparently will sterilize the local lesions but the long term results in individual patients are not known More recently a trivalent arsenical which is more active has been prepared under the name of STB A single daily oral dose of 0 01–0 02 Gm per kg body weight for five days has sterilized the local lesions and rendered the crabs painless A relapse rate of 7 per cent was found at five months Much more experience with this drug is necessary

condition involved may not be influenza This makes little difference particularly since many of the illnesses so treated run a course quite similar to that of influenza It is assumed that bacterial diseases will be recognized early and will be given the appropriate specific treatment

NONSPECIFIC TREATMENT

All patients should be isolated as much as possible Confinement of the patient even with mild illness has two principal objectives decrease of spread of the disease to others and decrease of the chance of exposure to pathogenic bacteria that are potential secondary invaders The patient is most comfortable in a moderately warm room This minimizes chilly sensations that accompany fever cool air aggravates coughing

In uncomplicated cases recovery is expected in one to seven days depending on the severity of the illness This may be followed for the more severely ill by a period of several days to weeks of lassitude easy fatigability sweating and palpitation on slight exertion There is no convincing evidence that tonics vitamins or hormone treatments effect any noticeable change in these symptoms The aged the debilitated and those with cardiac or other serious illnesses should return to normal activity only gradually to avoid undue strain on the circulatory system No patient should continue activity that is fatiguing A ritual of bed rest forced fluids liquid diet saline laxatives and prophylactic use of sulfonamides or penicillin to discourage secondary infection should be avoided except when specifically indicated

Persons with mild illnesses do not need to stay in bed but should be persuaded to stay in their rooms The more severely ill and those who are febrile will be more comfortable in bed Diet does not need regulation those who do not feel like eating will not starve during such a brief illness Fluids should be taken as desired. There is no good reason for forcing fluids this causes discomfort to the patient by precipitating repeated visits to the bathroom If constipation persists an enema can be used otherwise there is no purging

SYMPTOMATIC TREATMENT

The early symptoms of most concern to the patient—chilly sensations fever headache muscular aches and prostration—probably are due to some toxic property of the virus itself since experimentally they occur after injection of noninfectious virus in the form of vaccine Any temporary relief from the discomfort of fever and aching gained by use of acetylsalicylic acid in doses of 0 6 Gm may be offset by the resultant nuisance of profuse sweating However some patients prefer to have the drug Sweating not due to medication may occur at any time during the course of the disease and does not require attention except for changes of clothing and perhaps alcohol rubs although the latter are overrated

Some persons principally children have nausea vomiting or diarrhea at the onset or during the early course of illness No special treatment is required If these symptoms last much longer than one day the disease probably is not influenza

Pharyngeal irritation and cough result from viral invasion of the epithelial lining of the respiratory tract Cough often is nonproductive and may be frequent hacking and exceedingly distressing Codeine 15-30 mg by mouth every four hours if necessary usually controls the cough and also may give relief from malaise and aching Coryza or other evidence of rhinitis often does not occur early and when present is apt to signify bacterial secondary invasion Nasal vasoconstrictors will give only temporary relief from nasal obstruction Sufficient bronchitis and bronchiolitis are usually present to account for the râles most often detected at the lung bases

7. *Viral Infections*

HAROLD E. PEARSON

THERE is no specific therapy for most viral infections However statements frequently found in discussions of the subject such as No effective treatment has been devised—symptomatic therapy does not alter the course of the condition scarcely can be expected to offer any encouragement to the patient and are not strictly true It is possible to make the illness more tolerable for the sufferer and sometimes to prevent disaster by preparation for complications before conditions become uncontrollable Chemotherapy is specific at present for only a few related diseases usually considered in connection with viral diseases such as lymphogranuloma venereum ornithosis trachoma and inclusion conjunctivitis By comparison treatment of bacterial infections with chemotherapy is dramatically effective whereas there is a tendency to regard therapy for viral diseases as something devised by an exponent of voodoo Many conditions in medicine are handled successfully without benefit of specific therapy, there are many arrows in the therapeutic quiver and not all of them necessarily must be golden headed

Treatment should be designed for the individual case The status of the patient should be evaluated when he is first seen and his course anticipated if possible Complications which may be expected particularly secondary bacterial infections for which specific treatment is available, should be considered Occasionally it is desirable to prevent the latter by prophylactic chemotherapy Supportive care should be planned and necessary symptomatic treatment decided on

Influenza

THIS disease properly includes only the conditions caused by influenza virus of known types The infection assumes various forms subclinical mild or severe febrile illness with or without upper respiratory involvement It occurs when a variety of diseases common colds bacterial and unidentified respiratory illnesses febrile diseases of unknown etiology and epidemic nausea and vomiting are prevalent The diagnosis usually is made only when influenza is epidemic and many cases are occurring Consequently treatment must be started with the understanding that the

changes in larger bronchioles and bronchi, only small amounts of sputum are produced Larger amounts of sputum probably indicate more extensive lung lesions Multiple, punctate hemorrhages, and focal areas of softening found in the brain account for the delirium, stupor, mental depression, and other symptoms of cerebral involvement

SYMPTOMATIC TREATMENT

Symptomatic treatment includes bed rest which the patient usually welcomes The diet does not need regulation unless abdominal distention occurs The delirious patient can be given nourishment by nasal tube or parenterally Fluids are taken as desired Aching, malaise, and cough may be relieved by codeine in doses of 30 mg Nausea, vomiting or diarrhea are transient symptoms that usually do not require treatment Constipation is relieved by enemas urinary retention by catheterization Severely ill patients may be incontinent Rashes, epistaxis and albuminuria sometimes occur and should not cause alarm, nor do they indicate a need for special treatment Persistent insomnia may be disturbing as well as exhausting for the patient and can be overcome with 0 1 Gm sodium pentobarbital

SPECIFIC THERAPY

The use of convalescent serum has been supplanted by antibiotic therapy Sulfonamides are not useful Most strains of psittacii tested are sensitive to penicillin, but the treatment of human beings even with large doses has given variable results Aureomycin, terramycin and chloramphenicol are effective in the treatment of experimental animals and human beings It must be realized that although the treated animals recover, the agent may still survive and persist for long periods of time One may surmise that it also survives in humans either in a quiescent stage or with persistent production of symptoms such as arthralgia or of cough From one patient subject to recurrent attacks of coughing active virus was obtained repeatedly from the sputum during a period of eight years!

Aureomycin, terramycin or chloramphenicol may be given in an initial dose of 0 5–1 Gm followed by a daily dosage of 1–2 Gm Clinical improvement may occur within forty-eight hours after start of therapy but treatment should be continued for ten to fourteen days

Dengue

THIS rarely fatal mosquito-borne disease is much more variable in its clinical manifestations than is sometimes appreciated When it occurs in definite outbreaks in areas where it is known to be endemic, many cases are readily recognized However, for an individual patient the diagnosis may not be made during the early stages when the signs and symptoms do not differ from those of various acute infectious diseases Saddleback temperature curves and rashes described as characteristic of dengue often do not occur

The primary problem is to decide that the patient does not have some condition that requires chemotherapy such as typhus typhoid, scarlet fever, pneumonia, meningitis, or malaria When this decision has been made, management of the patient involves an attempt to provide symptomatic relief for definite complaints The acute stage of the disease lasts ordinarily not

SECONDARY INFECTIONS

Pneumonia

Any signs of consolidation in the lungs or any secondary rise in temperature means pneumonia usually caused by secondary bacterial invaders Pneumococcic infections are most common but the staphylococcic infections are most lethal Since influenza predisposes to bacterial pneumonia a vigilant effort must be made promptly to recognize and treat this commonest and most serious complication The routine use of sulfonamides or antibiotics for influenza patients to prevent pneumonia is not justified However it is advisable to give penicillin for this purpose to patients who are prone to have numerous or prolonged illnesses from respiratory infections and to those who are in poor physical condition because of age or disease

Encephalitis

Postinfectious encephalitis is a rare but troublesome complication It is not caused by influenza virus invasion of the central nervous system In regard to treatment and prognosis it is like the encephalitis discussed elsewhere that may follow various infectious diseases *

* See Chapter 20

Psittacosis

DEFINITE diagnosis of psittacosis can be made only by identification of the virus which is found usually in blood sputum or throat washings A presumptive diagnosis can be made by demonstration of a rise in titer of serum antibodies Animal inoculation or serologic procedures should always be attempted if possible but facilities may not be available or the tests may not furnish information early in the course of illness Sera from persons who have had lymphogranuloma venereum cross react with psittacosis antigen

The disease should be considered in connection with any patient who has nonbacterial pneumonia or who has an unexplained febrile illness and a history of exposure to an environment containing parrots parakeets or pigeons Occasionally chickens ducks or other birds have been sources of infection for human beings Sometimes such a history of exposure can not be obtained and the source of infection is unknown Person-to-person transfer of the virus has occurred and is always a possibility Patients should be isolated and attendants should observe strict isolation technic including the wearing of suitable masks such as the variety with flannel insert

The untreated disease is apt to persist for two or three weeks It has been reported fatal for ten to forty per cent of older persons but it rarely causes death in children or young adults Relapses may be expected in persons who have not been given adequate chemotherapy The early symptoms fever headache anorexia nausea fatigue drowsiness apathy and prostration may be due to the toxic properties of the virus Toxic effects can be demonstrated in experimental animals and small hemorrhages occur in various organs The latter perhaps induce the thrombi commonly found in severe infections and which may cause death by pulmonary thrombosis The scattered areas of infiltration in the lungs are associated with hyaline thrombi of capillaries and with considerable desquamation of the epithelial lining of small bronchioles Because of incomplete involvement of any given area of the lung and of slight

system Excessive muscular exertion can result in circulatory collapse Every effort should be made to encourage the patient during the periods of depression Pastimes should be arranged that will occupy the attention and that involve only slight or no physical exertion

Colorado Tick Fever

THE wood tick, *Dermacentor andersoni,* transmits this disease which has been recognized only in the Mountain States Probably the agent has a much wider distribution since it has been recovered from the common dog tick, *D variabilis,* obtained on Long Island One may expect that the disease will be diagnosed in many places when the possibility of its widespread occurrence is better known Because the illness runs a nonfatal course very similar to influenza or to dengue, the diagnosis is not made on a clinical basis, but only in retrospect by means of serological tests The etiology may be suspected because of a history of tick bite

TREATMENT

The management of the patient will be similar to that for influenza In this instance, however, one need not be so alert to detect bacterial invasion because complications of any type have not been reported This infection is not communicable from man to man by contact Recovery is usually rapid Early in the illness one should always consider the possibility of Rocky Mountain spotted fever, the rash usually seen in this disease does not occur in Colorado tick fever

Rabies

RABID dogs are the chief source of infection for human beings The management of rabies involves the immediate local treatment of all dog bites as well as the bites of other possibly rabid animals A decision must be made to give or withhold serum or vaccine therapy, complications of vaccination must be recognized and treated The invariably fatal human disease is rarely a problem

Many factors affect the development of rabies after a bite from a rabid animal The most important probably are the amount of virus deposited and the extent of the wound The incidence of the disease is greater and the incubation period is shorter after head bites than for bites elsewhere, perhaps because of penetration without interference from clothing into the relatively superficially located muscle tissues of the head The actual number of untreated persons who develop rabies after bites of proved rabid animals is not known but it is estimated not to exceed an average of fifteen per cent Because the disease is fatal, every person must receive the benefit of treatment if there is any reasonable probability that inoculation of virus has occurred

longer than one week, but convalescence may be prolonged for several weeks Except for rare mild illness, most persons will prefer to stay in bed during the acute febrile period A special diet is not necessary, fluids may be taken as desired The constipation commonly present may be relieved by use of enemas or of milk of magnesia 30 cc

SYMPTOMATIC TREATMENT

The most annoying symptoms for the patient are aching eye muscles, headache backache and pains around joints These perhaps are manifestations of toxic viral activity as also is fever The pathogenesis and tissue tropism of this apparently generalized infection are not known If the patient finds the fever too discomforting tepid sponge baths are indicated acetylsalicylic acid will add to the discomfort by producing sweating and may have little or no effect on the temperature It should be tried in doses of 0 6 Gm for temporary relief of discomfort particularly in the milder cases

Barbiturates such as phenobarbital 60 mg, may be given for sedation Sodium pentobarbital or seconal in 0 1 Gm doses is helpful at night if insomnia occurs The latter symptom is apt to persist even during convalescence Drugs should not be used so regularly or continuously that the patient becomes completely dependent on them for sleep The moderately and the severely ill person will obtain relief from the aching and pain only after considerable sedation which may be obtained by use of codeine in doses of 30 mg repeated every two hours

Epigastric pain, diarrhea or vomiting may occur the last commonly in children These do not require special treatment unless, as occasionally happens vomiting is persistent Morphine sulfate 15 mg, should control it Convulsions seen in children heart murmurs or such alarming symptoms as paresthesias or painful, stiff neck are transient

The development of a nonproductive cough accompanied by rales but without roentgenographic evidence of lung involvement may suggest pneumonitis However, bacterial pneumonia complicating dengue is rare Unless this diagnosis is definite, it is preferable to resist any temptation to treat it with chemotherapy

The severely ill patient may have epistaxis or hemorrhages subcutaneously or into viscera such as the kidney The mechanism of this bleeding is not known These symptoms are not persistent and special treatment is not required, except perhaps, nasal packs if the epistaxis is profuse The nature of the kidney lesion responsible for the albuminuria commonly found is not known Treatment is not indicated unless there is pre-existent renal disease which may be aggravated Hemospermia or orchitis may occur Testicular atrophy can develop when there has been little or no swelling Fortunately complications such as paresis of eye muscles iritis or keratitis are rare

After the acute episode of the first week, the patient may expect a period of days to weeks during which he feels lethargic and is fatigued by slight exertion He is irritable and feels depressed Such persons may have bradycardia—usually persistent since early in the disease—low blood pressure, both systolic and diastolic, and may complain of painful palpitation associated with extrasystoles It has been suggested although not established that these events result from involvement of the autonomic nervous system with development of vagotonia Atropine sulfate, 0 5 mg subcutaneously given with 60 mg of phenobarbital several times a day may give some relief

Return to normal activity should be gradual and not attempted faster than the patient can achieve without fatigue to prevent undue strain on the cardiovascular

system Excessive muscular exertion can result in circulatory collapse Every effort should be made to encourage the patient during the periods of depression Pastimes should be arranged that will occupy the attention and that involve only slight or no physical exertion

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LOCAL TREATMENT

In areas where rabies is present, an unprovoked bite that produces a laceration under any of the following circumstances should receive local treatment immediately to prevent the disease (1) the biting animal is clinically rabid (2) the biting dog is unknown and was not adequately observed (and was possibly rabid), and (3) the dog is known and has had recent sudden change in behavior (dogs probably have virus in the saliva during several days before definite signs of infection appear) Any wound contaminated with saliva from a clinically rabid animal also should be given local treatment The purpose of this treatment is to remove or to inactivate the virus at the site of deposition before there has been an opportunity for it to invade peripheral nerve fibers and to migrate centripetally along them

Clinical practice based on scant experimental evidence indicates that application of various chemicals as long as several hours after infliction of a wound tends to prevent infection with rabies Such measures may be useless even if applied immediately and any effectiveness decreases with time at an unknown rate Nevertheless, the patient should be treated as soon as possible and even after a delay for as long as forty-eight hours

The wound should be freely opened deeper than its base and ragged tissue and foreign material removed It should be irrigated thoroughly with 20 per cent Tr green soap Nitric acid treatment is painful if the wound is deep, local anesthesia should be used before it is applied The acid treatment results in scars and it should not be used on the face Tincture of iodine followed by irrigation with soap solution may be employed The last method perhaps is the best one presently available

Ordinarily persons should not be given tetanus antitoxin for animal bites and particularly not if there is any likelihood that rabies vaccine will be given The serum reactions that develop after use of antitoxin are apt to be confused with reactions to the vaccine

VACCINE THERAPY

The decision to use serum or vaccine therapy must be tempered by the knowledge that the former is effective experimentally but as yet has had only limited clinical trial Vaccine therapy is not well established experimentally and its clinical use has usually been under conditions that preclude any appraisal of the benefits since controls are lacking In the small series where untreated controls were observed vaccine therapy reduced the fatality rate by one half

Paralytic reactions, some fatal, to vaccine occur in as many as one in one thousand persons treated Vaccine should not be used unless a reasonable probability exists that the recipient has been inoculated with the virus This will include (1) persons with an unprovoked bite through the skin by any dog or suspected rabid animal that cannot be detained and observed for evidence of rabies (2) persons bitten by clinically rabid animals, (3) persons with a bite from any animal proved rabid by laboratory examination, (4) persons who have had any direct contact of their skin with saliva from proven rabid animals and (5) infants or small children who played with a rabid animal

If the biting animal is not observed and examined, or if the bite involved the head, treatment should be begun immediately If the biting animal is detained for observation, treatment need not be begun unless a diagnosis of rabies in the animal is established by laboratory examination Available evidence does not clearly indicate that a delay of two weeks in starting treatment reduces its effectiveness Because of short incubation periods for head bites, delayed treatment cannot be effective

There is little choice in vaccine therapy. None is satisfactory in the sense that it is highly protective and free from undesirable reactions. Vaccine is supplied in vials each containing a single dose of 0.5 to 2 cc depending on the product; it should be kept refrigerated until used. One injection is given subcutaneously in different areas of the abdomen daily for fourteen days. Claims for advantages to be gained from use of double doses or from treatment for longer periods are unconvincing. The duration of immunity induced by vaccination is not known but should not be considered to exceed six months.

Serum therapy is effective experimentally and should be used in addition to vaccine. It is most effective when used soon after virus injection and probably is without effect if given later than three days after the bite. A single dose of serum is given intramuscularly all or in part at the site of the bite. Theoretically this will inactivate virus present in the individual and should not interfere with the development of any active immunity stimulated by vaccination. The value of the serum exceeds the disadvantage of the resultant serum sickness which may be expected to occur in approximately 20 per cent of individuals treated.

Reactions to Vaccines

Reactions to vaccines result from sensitization to the brain tissue contained in them. Persons who receive a second or a third course of vaccine treatment are more apt to develop undesirable reactions than those who are given a single course; thus this is an occupational hazard for veterinarians. The routine use of antihistaminics to prevent such reaction has been suggested, but the effectiveness of the procedure has not been determined. Local reactions may occur a week or more after treatment is begun and consist of itching, pain, tenderness, erythema, or edema with wheals that develop in a few minutes to a few hours at the sites of injection and disappear before the next injection is due. Some persons develop more generalized rashes or urticaria. This type of reaction does not require treatment. However, if the person is too uncomfortable, he may be given one of the antihistaminic drugs in ordinary therapeutic dosage. Immediate generalized reactions of urticaria, angioneurotic edema, and syncope may be seen after any injection in persons who have been sensitized previously by a course of treatment. Relief from these symptoms is obtained by the subcutaneous injection of 0.3 cc. of epinephrine hydrochloride. Following such a reaction, a person may tolerate the remainder of the vaccine treatment given in regular or in repeated smaller doses. If similar reactions recur, vaccine treatment should cease.

Generalized Reactions. Generalized reactions may develop during the second or third week, and occasionally longer, after beginning vaccine treatment. Symptoms are quite variable, consisting of some combination of malaise, muscular pain, fever, headache, backache, nausea, diminished sensation, urine and feces retention, localized or progressive paralysis, drowsiness, apathy, and convulsions. All persons given vaccine must be observed carefully for evidence of these complications and injections must be discontinued as soon as any of them occurs.

Recovery sometimes is rapid within a few days but often is prolonged for weeks to months. Approximately five per cent die and survivors may have muscular weakness, tremor, ataxia, or mental change. It may be impossible to distinguish clinically these neuroparalytic accidents from rabies. A phase of excitement or symptoms of hydrophobia do not occur in the former. The patient should be confined to bed and given whatever food he will eat. If he cannot eat he may be fed through a nasal tube or nourished parenterally with glucose and amino acids. There is no advantage in forc

LOCAL TREATMENT

In areas where rabies is present, an unprovoked bite that produces a laceration under any of the following circumstances should receive local treatment immediately to prevent the disease (1) the biting animal is clinically rabid, (2) the biting dog is unknown and was not adequately observed (and was possibly rabid) and (3) the dog is known and has had recent sudden change in behavior (dogs probably have virus in the saliva during several days before definite signs of infection appear) Any wound contaminated with saliva from a clinically rabid animal also should be given local treatment The purpose of this treatment is to remove or to inactivate the virus at the site of deposition before there has been an opportunity for it to invade peripheral nerve fibers and to migrate centripetally along them

Clinical practice based on scant experimental evidence indicates that application of various chemicals as long as several hours after infliction of a wound, tends to prevent infection with rabies Such measures may be useless even if applied immediately and any effectiveness decreases with time at an unknown rate Nevertheless, the patient should be treated as soon as possible and even after a delay for as long as forty-eight hours

The wound should be freely opened deeper than its base, and ragged tissue and foreign material removed It should be irrigated thoroughly with 20 per cent Tr green soap Nitric acid treatment is painful, if the wound is deep local anesthesia should be used before it is applied The acid treatment results in scars and it should not be used on the face Tincture of iodine followed by irrigation with soap solution may be employed The last method perhaps is the best one presently available

Ordinarily persons should not be given tetanus antitoxin for animal bites and particularly not if there is any likelihood that rabies vaccine will be given The serum reactions that develop after use of antitoxin are apt to be confused with reactions to the vaccine

VACCINE THERAPY

The decision to use serum or vaccine therapy must be tempered by the knowledge that the former is effective experimentally but as yet has had only limited clinical trial Vaccine therapy is not well established experimentally and its clinical use has usually been under conditions that preclude any appraisal of the benefits since controls are lacking In the small series where untreated controls were observed vaccine therapy reduced the fatality rate by one half

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blocking of the eustachian tubes Recovery occurs within a few days

Bacterial sinusitis and otitis media are common complications particularly in infants and children Bacterial pneumonia occasionally develops All must be promptly diagnosed and treated as described elsewhere Sulfonamides or antibiotics should not be used routinely for prophylaxis of bacterial invasion because they usually are not required and there is always risk of sensitization The drugs are not effective against the virus—or possibly the viruses—of the common cold They should be used prophylactically, however, for patients who, from previous experience, are known to be prone to have bacterial complications and for those who are suffering from some serious illness Bacterial vaccines will not prevent the common cold Neither are they effective for protection against the bacterial complications of colds Occasionally a patient who is subject to frequent upper respiratory infections will have fewer attacks while receiving these vaccines Usually, however, they are not of observable value

TREATMENT

There is no good treatment for colds Sweating, forcing fluids, alkalinization, purging serve to divert the patient s attention He will be most comfortable if at rest, but not necessarily in bed, in a moderately warm environment Acetylsalicylic acid in doses of 0 6 Gm and mild sedation with phenobarbital 0 1 Gm are helpful for the malaise and general discomfort Heavy sedation is contraindicated because it is apt to promote accumulation of secretions in the bronchi and to predispose to pneumonia The most annoying symptoms of nasal discharge and obstruction are temporarily relieved by use of several drops of 0 25 per cent "neo synephrine" in saline instilled in each nostril or by use of a vasoconstrictor inhalator every two hours These procedures predispose to bacterial invasion of the sinuses Antihistaminic drugs are not curative but may give some symptomatic relief and control the nasal discharge, however, they also have the disadvantage just mentioned Coating the nostrils and lips with petrolatum will prevent chapping

Colds are readily communicable to others for a period of several days and particularly during the first few days after onset of symptoms The disease is spread by the respiratory route, chiefly as a droplet nuclei infection Patients should be urged to stay home to limit transmission of the illness Attempts to prevent familial infection by devices such as masks or by room isolation usually are fruitless

Measles

MEASLES is a systemic infection with localized involvement of the skin mucous membranes, and the lungs The effects produced are closely associated with vascular changes The eruption consists of capillary congestion, perivascular round cell exudate, and edema The last is particularly noticeable as swelling of the face The superficial epithelium overlying the affected areas desquamates but healing occurs without scarring There is some necrosis in lesions of the mucous membrane such as Koplik spots In the most severe form of the disease there are hemorrhages into the lesions which may become confluent in the skin and cause bleeding from all mucous membranes There is bronchitis with purulent exudate and sloughing of epithelial

ing fluids, particularly since it may be necessary, by means of repeated catheterization, to relieve urinary retention resulting from myelitis, a procedure which may cause urinary tract infection Fecal retention may be treated with enemas

These patients often require sedation to relieve the severe pain experienced in connection with neuritis or myelitis Phenobarbital, 60 mg, and codeine, 60 mg, are useful Patients also are prone to develop bed sores and pneumonia Careful attention must be given to care of the skin Change of position and deep breathing help prevent atelectasis Chemotherapy should be used promptly if pneumonia develops. Physiotherapy is useful to improve neuromuscular function and should be started as soon as it can be tolerated

SUPPORTIVE TREATMENT

Once the clinical diagnosis of rabies is made in a patient, there is only one objective in treatment—to relieve the often intense mental anguish and physical pain of the doomed victim during the few days of survival after onset of symptoms Unfortunately some patients with the paralytic form of the disease linger for several weeks before death Mental alertness may persist until the end Anxiety and sense of impending death can be prominent Intermittent spasm of muscles of deglutition or of other muscles may be precipitated by only slight physical or mental stimulus, clonic, generalized convulsions are apt to be extremely severe

The patient should be kept in bed under continuous sedation attained with repeated hypodermic injections of morphine sulfate, 30–60 mg or sodium phenobarbital, 0 6 Gm, or by 0 2 Gm sodium pentobarbital intravenously Some patients are not sedated by use of morphine

A darkened room as free as possible from visual and auditory stimuli should be utilized Use of restraints may be necessary at the onset of convulsive seizures Nutrition and hydration are maintained by fluids given intravenously and by clysis Sometimes fluids can be swallowed without difficulty or one fluid such as milk can be taken even though water cannot Catheterization and enemas may be necessary

Attendants should beware of contamination by virus in the saliva that may drool more or less continuously from the mouth of the patient Some patients will spit at attendants Rubber gloves and a gown should be worn Articles soiled by any body discharge from the patient should be sterilized preferably by heat

Common Cold

THIS viral disease often is not readily differentiated from other upper respiratory infections or from allergic rhinitis The symptoms of sneezing coryza, malaise, and lassitude with or without slight fever are common to all and result from involvement of the mucous membranes of the upper respiratory tract Some hyperemia of the conjunctivae, nose, and pharynx may be seen in any of these conditions and nasal obstruction likewise is nonspecific Pale, edematous nasal mucous membranes sometimes are seen in allergic rhinitis and eosinophiles may be found in nasal smears itching of the palate is characteristic of the condition A moderate or severe sore throat, aching, and leukocytosis are apt to occur with bacterial infection The person with a cold has only a slightly sore throat The principal symptoms are sneezing, watery nasal discharge, and lassitude, after one day there is nasal obstruction and

appearance of the rash Intramuscular doses of convalescent serum, 2 cc, or gamma globulin 0 05 cc per Kg body weight are given Up to 50 cc of serum or 5 cc of globulin are used This passive protection lasts approximately three weeks and must be repeated if it is desired to secure protection against subsequent exposures

MODIFICATION

Modification cannot be achieved by any set procedure The modified disease tends to have an incubation period prolonged to as much as one month a milder course, and fewer complications In general 20 cc of convalescent serum is *given* on the sixth to eighth day after exposure, 50 cc on the ninth and tenth day and 100 cc intravenously on the eleventh day or until the rash Gamma globulin may be tried in amounts up to 2 cc on the basis of 0 01 cc per Kg body weight It is given on the sixth or seventh day after exposure Larger doses up to 10 cc are given if treatment is instituted later Gamma globulin should never be given intravenously because of its colloidal nature Attempted modification in the period up to eight days may result in prevention, a small percentage will have the unmodified disease Modification in later periods is quite unpredictable but succeeds sufficiently often to justify the attempt for those who are ill from other diseases and for those who are debilitated Persons who have the modified disease presumably have a resultant permanent active immunity

Reactions to convalescent sera are few There is transient local pain and tenderness The danger that a serious reaction in the form of serum hepatitis that may develop two to seven months later is partially avoided by use of irradiated serum After gamma globulin therapy there may be transient, local soreness and an occasional person will have a febrile reaction which is of short duration

SYMPTOMATIC TREATMENT

The therapy of measles after onset of symptoms is directed to symptomatic relief and to prevention or prompt recognition and treatment of bacterial complications Beginning the second day after onset of symptoms, procaine penicillin 300 000 units once daily, is given to all patients under 15 years, and to adults who are debilitated for any reason This is continued for five days The drug does not have any effect on the virus but is given prophylactically against bacterial infections it is not used routinely for adults because such complications for them are rare and are not so *serious Serum therapy has little or no ef*fect when given after the rash appears and is not used

The malaise, chilly sensations fever headache, and prostration—sometimes with muscle aches—seen in the prodromal period usually are sufficient to make the patients prefer bed rest However, if they do not, there is no necessity of imposing it on them, provided they are isolated and not allowed visitors who may carry pathogenic bacteria to them In the home this would mean exclusion of nonfamilial persons as well as room isolation from familial members who have respiratory infections Since the patient may be infectious for others during the period from four days before to five days after onset of rash susceptible persons particularly young children, should be kept from contact Persons who are inadvertently exposed should be managed as previously described Since approximately 90 per cent of exposed susceptibles will contract the disease it is desirable to expose those over 5 years of age for the purpose of giving them the modified disease under controlled conditions provided that circumstances permit their management if measles develops

Those who have elected bed rest may resume activity within the confines of their area of isolation as soon as they feel like it,

cells which may occlude the bronchus The inflammatory process extends into the peribronchial tissue to produce areas of pneumonia The pneumonitis predisposes to secondary bacterial pneumonia, this formerly resulted in most of the deaths from measles chiefly during the first five years of life

As many as 50 per cent of patients experience middle ear involvement as shown by hyperemia of the membrane or by catarrhal otitis media Here also viral invasion predisposes to bacterial secondary infection Purulent otitis media is the most common complication of measles and may occur as often as every fourth case seen in childhood

Catarrhal laryngitis may produce symptoms of hoarseness and loss of voice and even signs of obstruction such as inspiratory stridor and cyanosis this usually improves with onset of the rash Occasionally laryngitis persists as a result of bacterial invasion Bacteria sometimes penetrate the mucous membranes of the nose and throat to produce cervical lymphadenitis However there is a general lymphoid tissue reaction to the virus but only to a slight degree, with some hyperplasia and production of the giant cells of Alagna characteristic of this disease The mechanism of this reaction is not known nor is there any understanding of the reasons for development of leukopenia Fortunately the severe catarrhal inflammation of the conjunctivae only rarely has sequelae in the form of bacterial infection that produces purulent conjunctivitis or corneal ulceration

ENCEPHALITIS

The most serious complication of measles is encephalitis which occurs perhaps once in ten thousand or more patients it appears more often in some outbreaks than others possibly because of differences in strains of virus Rarely is it seen in adults Ten per cent or more of the cases are fatal and as many as one in three have residual psychic or neurologic changes This encephalitis is not the result of direct viral infection of the central nervous system but is a hypersensitivity reaction similar in pathology to other types of postinfectious encephalitis *

The risk of congenital anomalies resulting from measles contracted during the first trimester of pregnancy is not known Spontaneous abortion or stillbirth frequently occur in any period of pregnancy Fetal infection has been reported in infants delivered of mothers who had the disease near term

PROPHYLAXIS

Measles never should be considered to be a mild illness since any child and especially those under 4 years of age, may have the more severe forms of the disease and adults seldom have a mild type Prevention of the disease should always be attempted for children under 5 years who have been exposed to the disease and for those who are sick or debilitated Modification of the disease should be tried for most other persons who have known exposure This is obtained from use of convalescent serum or of gamma globulin The globulin contains the antibodies concentrated twenty five times from pooled plasma of normal adults The great majority of adults have antibodies as a result of previous infection Although the results obtained with the two products are almost equally good, the gamma globulin is preferable because of smaller volume more uniform potency and freedom from the agent of serum hepatitis and from the sensitizing Rh antigen If sufficient antibody in either form is given even as late as five days after exposure the disease will be prevented in most individuals The disease is communicable four days before to five days after

* See also Chapter 20

perature headache, and stiff neck with some combination of stupor, delirium con vulsions and pareses There is no specific treatment the general treatment is dis cussed elsewhere *

The severe type of measles with marked prostration, hemorrhages, and circulatory collapse has a poor prognosis despite heroic attempts at supportive treatment which should include inhalation of oxygen with 5 per cent carbon dioxide and re peated transfusion

* See Chapter 20

German Measles

THIS disease ordinarily is mild with some fever malaise coryza sore throat and en largement and tenderness of the postau ricular occipital and posterior cervical lymph nodes The rash that appears at any time up to five days after onset is variable in extent intensity and type of eruption It may fade rapidly so that the appearance can change in a period of few hours and usually disappears within two or three days There may not be any rash The systemic disease with involvement of the skin and mucous membranes is similar to mild measles but there is at most only moderate hyperemia of the conjunctivae without pho tophobia There is no grossly recognizable otitis media or pneumonitis Recovery usually is complete within two to four days ("three day measles")

A few persons will have recurrence of symptoms even with rash two to six weeks after the first episode There is no good explanation for this perhaps the virus per sists and is reactivated because antibodies have not yet developed Presumably the active immunity resulting from infection is of long duration since recognized second attacks of the disease are rare Young chil dren and adults have the most severe ill ness The former are also more prone to have complications such as bacterial sec ondary pneumonia and otitis media The incidence of the encephalitis that develops on the fourth to sixth day after onset of illness is unknown but is estimated to be 1 5000 to 1 10 000

INFECTION DURING PREGNANCY

At present there is no satisfactory answer to the problem of German measles that occurs in a woman during the first trimes ter of pregnancy The originally reported high incidence of congenital defects in the offspring of such persons has not been con firmed in all subsequent studies This phenomenon may not occur with all strains of the virus and perhaps with only certain variant ones Since sufficient data are not available to permit an estimate of the actual risk of congenital defects resulting from German measles and since the diag nosis of the disease often cannot be made with any surety, abortion is not justified as a prophylactic procedure Women who have the disease later in pregnancy occasionally abort spontaneously or have a stillbirth

PROPHYLAXIS

Prevention of German measles by use of immune serum or of gamma globulin has not been satisfactorily evaluated The re sults so far are not encouraging Because the disease is so mild prevention or atten uation usually is not indicated If preven tion is attempted 30 cc of convalescent serum are given intramuscularly as soon as possible after exposure

and any patient may be allowed to return to normal activity any time he desires it seven days or more after onset of the rash All patients should be kept in a moderately warm environment whether indoors or out to avoid aggravation of symptoms of coryza and cough Nose drops of neo-synephrine," 0 25 per cent in saline, or vasoconstrictor inhalator are helpful for the former

Bright or direct light should be avoided because of the photophobia and not be cause of any relationship to conjunctivitis it is not necessary to have a darkened room Malaise and discomfort from fever are relieved with aspirin phenacetin-caffeine compound 0 6 Gm repeated as necessary Anorexia commonly occurs early and may persist until the rash appears Nourishment best is given as liquids These are replaced by semisolid and solid food when they are acceptable to the patient Nausea may be present early and sometimes persists for several days and is accompanied by vomit ing Such persons are given nothing by mouth except sips of water, parenteral nu triment and fluids are provided Phenobar bital, 0 1 Gm is helpful

Diarrhea may be marked particularly in younger children and if uncontrolled can lead to death It is not known whether this represents direct viral invasion of the ali mentary tract or a reaction to the general ized infection Constipation is not usually a problem, but if it occurs it may be re lieved by milk of magnesia 30 cc

If the cough is exhausting to the patient or interferes with sleep codeine phosphate 30 mg may be administered The edges of the eyelids and nares should be coated with petrolatum and kept free of crusted secre tions that tend to accumulate and serve as a nidus for bacteria Herpes commonly occurs For this complication zinc oxide paste may be applied Laryngeal complica tions can be sufficiently severe to threaten complete obstruction but only rarely is it necessary to have an intubation or tracheotomy These procedures should be the last resort The laryngitis may be expected to improve when the rash appears and ordi narily does not require special treatment Catarrhal otitis media almost never re quires drainage Chemotherapy will pre vent purulent otitis media only rarely will this develop and require myringotomy An evanescent, erythematous rash that may appear during the prodromal period should not lead to confusion in diagnosis with scarlet fever The marked coryza Koplik spots, and leukopenia of measles are not seen in scarlet fever The mechan ism of this vascular phenomenon has not been explained One might suspect that a capillary active toxin is associated with the virus

Rash

The rash of measles appears two to four days after onset of symptoms and often is accompanied by a marked remission of the latter Itching usually is not pronounced and can be relieved by application of phenolated calamine lotion The rash gen erally fades after one week and there is a fine desquamation of skin from the lesions but pigmentation will persist for several weeks The temperature which may have declined even to normal before the rash can be seen, begins to rise again when the rash appears and then rapidly or more often gradually returns to normal after a variable period of hours to days In the absence of complications the patient may feel quite well despite the fever and rash If the temperature remains elevated and there is an increase in the rates of the pulse and respiration together with signs of pul monary consolidation, bacterial pneumonia is present and should be treated promptly Scattered râles but not signs of consolida tion may occur with the viral pneumonitis Encephalitis begins during the week after onset of rash and may be seen even in otherwise mild cases There is a rise in tem

Mumps

MUMPS virus affects principally glandular and nervous tissue The symptoms are related to the organ involved and the process may involve several organs simultaneously but more often will extend from one organ to another during a period of several days up to two months A patient will feel quite well and ready to resume normal activity only to relapse as a fresh site is invaded

GLAND INVOLVEMENT

The symptoms of gland involvement result presumably from parenchymal invasion by virus with secondary vascular injury that produces marked edema and small hemorrhages in and around the gland A mononuclear cell exudate has been described in the salivary glands There is a remarkably small amount of necrosis, and healing occurs without much scarring The swelling usually subsides in a few days but may persist for two weeks In the testes areas of destruction of convoluted tubules and polymorphonuclear cell exudate are found adjacent to normal areas There is considerable edema of the interstitial connective tissue, the tunica albuginea, and the tunica vaginalis with the production of a hydrocele by the severe infections Some testicular atrophy occurs in approximately one half of untreated persons who develop orchitis This results perhaps in part from direct viral destruction of tissue but probably mainly from pressure necrosis since relief of the pressure prevents much atrophy Even when atrophy does occur it usually is unilateral and only rarely has sterility been reported When the salivary glands are affected saliva production may be normal or slightly diminished With pancreatic involvement, function of the gland is not impaired

COMPLICATIONS

One half to two thirds of patients have *meningitis* or *meningoencephalitis* as shown by pleocytosis of the cerebrospinal fluid and 10 to 30 per cent of patients will have clinical signs of nervous system involvement, this may occur as the only manifestation of mumps and is the most common type of aseptic meningitis As many as 15 per cent of patients may have myocarditis Occasionally there is precordial pain dyspnea, palpitation and marked bradycardia More frequently there are no symptoms and the diagnosis is made from electrocardiographic changes which may return to normal within a week or persist occasionally for several months ECG tracings should always be taken on adults to detect these changes It is not known if this represents direct viral invasion of the myocardium or results from some undiscovered toxic property of the virus Likewise unknown are the mechanisms of the seldom seen transient conjunctivitis keratitis and neuritis of the optic or facial nerves labyrinthitis may result in permanent deafness This can develop rapidly without premonitory symptoms or may be preceded by slight dizziness or ringing in the ears

SYMPTOMATIC TREATMENT

The management of mumps consists of providing relief for symptoms as they occur There is no convincing evidence that physical activity either during the incubation period or after onset of symptoms has any effect on the disease However, because of the occurrence of myocarditis it is prudent to keep most patients in bed during the acute phases of the disease and confined to their rooms for at least several days after they are symptom free The moderately or severely ill patient will appreciate

SYMPTOMATIC TREATMENT

The treatment of the disease is entirely symptomatic Chemotherapy does not affect the virus Often the diagnosis is not made until the rash appears The patient should be isolated during the period of acute illness to protect him from potentially pathogenic bacteria that might be acquired from other persons The disease is communicable to others during the period from one day before until five days after onset of symptoms Susceptibles in whom the disease is not desired should be excluded from contact with the patient during this period Bed rest is not necessary, but the patient may prefer it. No special attention needs to be given diet fluid intake, or excretion Acetylsalicylic acid, 0 6 Gm , may be given every three or four hours for malaise or general discomfort Young children should be observed closely for evidence of bacterial complications otitis media or pneumonia The encephalitis that develops is not a primary viral encephalitis and is treated similarly to the postinfectious encephalitis described elsewhere

Exanthem Subitum (Roseola Infantum)

THIS disease is important because it is common in children during the first two years of life and is often confused with measles or German measles It rarely is seen in older children and not in adults Although second attacks occasionally occur, they are unusual The etiologic agent probably is a virus although this has not been proved The disease seen in infants probably results from the first exposure to an agent that is carried by many adults any illness it may produce in the latter group has not been recognized

The symptoms often are alarming with marked irritability, refusal of food, and temperature as high as 105° C Convulsions are not uncommon Sometimes there is moderately severe diarrhea The tympanic membranes, the conjunctivae, and the throat may show slight hyperemia which becomes more prominent after the rash appears Lymph nodes and spleen may be enlarged, but this is of little diagnostic use

After three or four days of sustained fever the temperature drops to normal, often precipitously or sometimes during the course of a day A morbilliform rash may be noted to have appeared suddenly after the fall in temperature, occasionally it is not seen until one or two days later The rash disappears, often within two days and less often, during the course of a week. The child usually appears to feel better after the rash is present and apparently recovers completely within the next two or three days Complications are rare, bacterial pneumonia seldom occurs Postinfectious encephalitis has been reported but the incidence is not known

TREATMENT

The management of the illness consists essentially of obtaining a correct diagnosis by excluding other diseases such as otitis media, meningitis, pneumonia, urinary tract infection, or enteritis reassuring the parents concerning the diagnosis and prognosis and lack of need for chemotherapy, and doing little to the patient The patient should be offered fluids and liquid nourishment, but they should not be insisted on if they are refused Acetylsalicylic acid has only a temporary effect on the temperature and need not be given Convulsions should not cause alarm and will respond to cooling measures such as a tepid sponge bath

den or may be gradual over the course of a day. There is apt to be considerable drainage during this period; the drain may be removed when this has diminished.

If surgical incision is performed late after the inflammation has begun to subside, little benefit is achieved. Almost all who have the operation develop only minimal atrophy detectable as a slight, persistent softening of the gland. Operation is not indicated for epididymitis even though there may be some hydrocele fluid. Sedatives such as codeine or morphine are preferable to refrigeration anesthesia in the form of an icebag applied to the affected parts.

Ovaritis

Ovaritis occurs less often than orchitis and is seen occasionally in postpubertal females. The symptoms are similar to those previously mentioned for orchitis but in women the pain and tenderness is principally in the lower abdominal quadrants with radiation to the umbilicus or to the lumbar regions. A menstrual period may be precipitated. No special treatment is necessary other than sedatives or analgesics for pain. Sterility has been recorded only for a few persons. The value of diethylstilbestrol and testosterone propionate in the treatment or prevention of orchitis and ovaritis respectively has not been established.

Pancreatitis

Pancreatitis occurs occasionally with constant or intermittent epigastric or left upper quadrant pain and tenderness, fever, nausea, and vomiting which may persist during the few days that symptoms continue. Either diarrhea or constipation prevails. The finding of elevated serum diastase levels is not useful as a diagnostic procedure here since it can result from parotid involvement. Blood sugar levels are not disturbed nor does alteration of pancreatic function occur as a result of infection. The patient is nourished parenterally until vomiting stops. Constipation is relieved by enemas. Diarrhea is self limited and of such short duration that it does not require special treatment. Pain is relieved with codeine or morphine.

Occasionally transient and usually mild lymphadenitis or inflammation of glands such as the breast, prostate, thyroid, Bartholin's, or the lacrimals is observed.

If it is desired to attempt to prevent spread of infection, the patient should be isolated but it must be realized that persons can be sources of infection for one or two days before onset and for approximately one week after onset of symptoms. Convalescent serum used to prevent or to treat the disease is so irregularly effective that its use is seldom justified. When the gamma globulin fraction of convalescent serum is given intramuscularly in a dose of 20 cc. and is used early, the incidence of orchitis is reduced by more than one half. If this product is available, it should be tried for males past puberty. Convalescent serum is less effective than its gamma globulin fraction for prophylaxis of orchitis and should not be employed unless an irradiated product is available. Otherwise there is too much risk of transmitting serum hepatitis through the serum. An intravenous injection of 50–100 cc. is given

bed rest, persons with only mild illness may be kept on reduced activity but not in bed The pain and tenderness associated with salivary gland involvement is lessened by application of heat by use of a hot water bottle or by cold in the form of an ice bag Since chewing and talking add to the discomfort both should be avoided A liquid diet can be given until the patient can manage to ingest semisolid food There is no need to force fluids fruit juices and sour foods should be avoided Antiseptic mouth washes and gargles are not necessary Aspirin phenacetin-caffeine compound with codeine 0 6–0 9 Gm in repeated doses helps relieve local discomfort and general malaise Secondary bacterial infection of the salivary glands with abscess formation is an extremely rare complication that should be treated promptly with chemotherapy

Meningitis and Encephalitis

With meningitis or encephalitis some combination of fever severe headache stiff neck dizziness vomiting, delirium, and coma occurs These symptoms usually last only a few days and recovery is prompt Death or sequelae are extremely rare Commonly some recurrent headache and transient dizziness may be precipitated by physical exertion during several weeks It may be difficult to determine the presence of a stiff neck when there is marked parotid swelling In the absence of salivary gland involvement, it is particularly important to differentiate tuberculous and mumps meningitis Most of the latter patients will develop specific complement fixing antibodies which may sometimes be detected as early as five days after onset Serum should be obtained for test as soon as possible after onset of illness and again at intervals of three to four days a rising titer is presumptive evidence of infection with mumps virus if the test is still negative two to three weeks after onset mumps usually may be excluded

If the headache of meningoencephalitis is so severe that relief is not obtained by use of acetylsalicylic acid or codeine, spinal fluid drainage by lumbar puncture is helpful If there is no salivary gland involvement patients with meningitis may have a regular diet If they cannot eat because of vomiting delirium, or coma, nutrition and fluids are given parenterally or by nasal tube

Orchitis

Orchitis begins with generalized symptoms of malaise, chills fever, headache, and backache followed within the next twenty four hours by a painful tender swelling of the testis which rapidly becomes more marked and which subsides gradually during the course of four to ten days Twenty to thirty per cent of males past puberty will develop this distressing type of the disease Ten to twenty per cent will have bilateral involvement The epididymis may also be affected with or without infection of the testes In the latter event the course is similar to but milder than with orchitis

The scrotum should be supported by a suspensory bandage Codeine in 60 mg doses helps relieve the pain Any patient who has more than a mild orchitis and who develops much pain and swelling of the testis should have the benefit of early surgical intervention This can be done easily the skin is aseptically prepared, infiltrated with 2 per cent procaine and an incision 1–2 cm in length is made on the anterior surface of the affected side to expose the tunica vaginalis This membrane is grasped with clamps or forceps and incised, fluid spurts out A small drain is placed beneath the tunica vaginalis and the wound is closed It is not necessary to incise the capsule of the testis, the tunica albuginea Relief of symptoms often is dramatically sud

the second day of the exanthem Labora tory tests are helpful early Sometimes the elementary bodies or viral particles of variola or vaccinia can be demonstrated by special staining of lesion scrapings The viruses of variola or vaccinia may be iso lated from the lesions by inoculation of embryonated eggs or may be identified from serologic tests using vesicle fluid or crusts as antigens Chickenpox virus does not react in this manner

The other diseases most apt to be con fused with chickenpox are generalized vac cinia which may be differentiated by the methods just described, generalized herpes zoster, and impetigo Zoster is closely re lated to chickenpox so that persons ex posed to one disease may develop the other Localized zoster differs clinically, general ized zoster is treated similarly to chicken pox

CONTAGION

Persons with chickenpox are highly in fective for others for a period of approxi mately one day before and six days after onset of symptoms Transmission is by droplet nuclei which are air borne Unlike smallpox, the crusts of chickenpox do not contain enough active virus to be a source of infection The patient should be strictly isolated if it is desired to prevent infection of others Attempts at isolation often fail in hospitals or institutions and usually are not worth while in the home

TREATMENT

The aims of treatment are to provide symptomatic relief and to prevent or to treat complications promptly, there is no drug that is active against the virus Bed rest is not necessary unless the patient pre fers it or unless there are complications Diet, fluid intake, and elimination do not require special attention unless the patient becomes constipated from being in bed Aching and discomfort are relieved by acetylsalicylic acid in doses of 0 6 Gm Itching is the principal complaint and can be relieved by applications of phenolated calamine lotion Patients should be warned not to scratch the eruption, scratching pro motes secondary infection and scars result if crusts are prematurely removed It is well to trim short the patient s nails and to use arm splints for young children If pustules are noted they should be opened and anti biotic ointment applied When numerous pustules appear it is preferable to give penicillin parenterally until they have regressed

Parenteral penicillin rarely is indicated prophylactically and then only for persons who have pre existing skin lesions or who are extremely ill or debilitated from an other disease Often the wall of a vesicle is so opaque that it looks like a pustule, but when incised the contents are not purulent When the eruption is present on the con junctivae ophthalmic aureomycin oint ment is used until healing has occurred If there is keratitis, the pupil should be kept dilated and the eye protected from light iritis or iridocyclitis may occur

The treatment of chickenpox pneumonia is supportive, chemotherapy is not helpful Bacterial pneumonia or otitis media should be treated promptly by chemotherapy The treatment of encephalitis is described elsewhere *

* See Chapter 20

Chickenpox

CHICKENPOX is a systemic infection with involvement principally of the skin and with a variable degree of invasion of the mucous membranes and of the epithelium of viscera. The lesions of the skin develop rapidly and consist of papules, vesicles with or without surrounding erythema, and crusts into which the vesicles are converted. Some papules do not become vesiculated. The prickle cells of the epidermis become swollen and liquefied, a crust forms after the fluid from the vesicle is resorbed or the vesicle is ruptured. The crusts drop off after a few days. There is slight, moderate or marked inflammation at the base of the lesion.

Chickenpox generally is a mild disease in childhood; symptoms may be few and only few scattered pocks appear. Even in an instance of average severity the child may not complain and will deny that he is ill. The rash can develop without any prodromal symptoms. More often there is fever, headache, backache and variable muscular aching; this lasts up to two days before a rash appears. During the first twenty-four hours there may be a transient diffuse, erythematous rash. The regular eruption appears any time after onset of symptoms and successive crops of vesicles develop within a week to ten days. The height and the duration of fever are variable. Any secondary rise in temperature results from complications such as bacterial infection or encephalitis. In the absence of complications, symptomatic recovery is rapid after the rash is fully developed.

Complications

Usually only the epidermis is involved in the skin lesions so that healing occurs without scarring. A few lesions may extend to include the corium. Secondary bacterial infection in the lesions also will cause this, resulting in a depressed scar. Such infection is the most common complication of the disease and if hemolytic streptococci are the invaders, erysipelas may occur. Bacterial otitis media and pneumonia only rarely occur.

Transient nephritis is observed in severe forms of the illness and occurs at any time up to three weeks after onset. There are red blood cells and albumin in the urine. Pneumonitis from viral invasion of the lungs occasionally is found in the form of patches of infiltration. When these are extensive, death is likely. There is marked interstitial inflammation and hemorrhage. The pneumonia resolves slowly and may persist for three to four weeks.

Encephalitis, myelitis and peripheral neuritis only rarely develop but are the most serious complications of the disease. They occur any time up to several months after onset but most often within the first two weeks. Approximately 10 per cent die and a similar number have sequelae in the form of muscular weakness, tremors or incoordination. Because of the histologic changes that have been reported in the brain, it is generally accepted that the condition is a form of postinfectious encephalitis. Chickenpox seldom results in abortion in pregnancy. Usually a normal infant is delivered. Rarely the child may be born with the disease.

DIFFERENTIAL DIAGNOSIS

From the standpoint of public health it is essential that every case is rapidly differentiated from smallpox. This may be difficult early in the disease or when the eruption is sparse or atypical. Usually the diagnosis can be made from the appearance of the polymorphous rash that is present by

fluent Hemorrhagic tendencies may develop with bleeding into the skin lesions and from the mucous membranes There may be considerable edema of the skin particularly of the face The patient may be quite lethargic or become delirious, convulsions are usual in children The case fatality may be as high as 30 per cent

TREATMENT

The patient should be isolated in order to prevent spread of the disease and to provide symptomatic relief The patient is infectious for others from the onset of symptoms until the disappearance of all scabs and crusts The environment may remain contaminated for a prolonged period even after removal of the patient, since virus is viable in crusts for as long as *one year at room temperature* The disease is most communicable in the early stages Articles of clothing eating utensils, or other things contaminated by the patient should be *sterilized preferably by heat* The environment should be thoroughly cleaned and disinfected after removal of the patient Strict isolation obviously is essential and in the absence of epidemics the sporadic case is best managed at home or at least not in a hospital in order to avoid risk of exposure to many persons

The moderately or severely ill patient will welcome bed rest This is not necessary for the mildly ill During the initial stages of the disease, pain and malaise may be the principal complaints These may be relieved by codeine or morphine Vomiting or diarrhea may be troublesome but usually subside at the time of the rash With the appearance of the eruption and particularly during the pustular stages itching of the skin and associated insomnia are the principal complaints Phenolated calamine lotion may be applied Dover's powder in a dose of 0 6 gm is helpful The patient *should be instructed to avoid scratching* since this leads to scarring Children should have their nails trimmed short and small children at least have arm splints applied. Air mattresses may make the patient more comfortable as will also a supporting frame for the bed clothes Frequent warm tub baths help to alleviate the itching Sometimes starch baths also are useful Petrolatum applied to the crusts tends to prevent their *flaking* and cracking open

Oropharyngeal lesions may be so extensive as to prevent or discourage the patient from eating Excessive salivation can be annoying There may be so much laryngeal edema as to require tracheotomy The patient is best given a fluid diet during this period *This will be followed by a soft diet* and a regular diet when they can be taken Conjunctivitis is usual and may develop into severe forms of eye disease such as *panophthalmitis It is well to apply petro*latum to the edge of the eyelids to prevent crusting and sticking aureomycin ophthalmic ointment may be used several times *daily to the conjunctivae as prophylaxis* against secondary bacterial infection The drug itself does not seem to be effective against the virus

It is prudent to use penicillin parenterally for its prophylactic value against secondary bacterial infection in any form and particularly against secondary bacterial infection in the skin although the pustule primarily results entirely—or at least initially—from virus activity By the time the patient is free from scabs he usually feels sufficiently well to resume ordinary activity

COMPLICATIONS

Complications include occasional otitis media and cellulitis or erysipelas which develop in connection with secondary bacterial involvement of skin lesions A *permanent alopecia occurs* rarely Postinfectious encephalitis occasionally is noted usually five to fourteen days after onset This is not due primarily to virus invasion *of the central nervous* system but is a hypersensitivity reaction

Smallpox

THE differential diagnosis of smallpox may be extremely difficult during the first few days of the disease and even during the first day or so after the eruption appears The diseases chiefly confused are *chickenpox, generalized vaccinia*, generalized herpes—simplex or zoster—and occasionally lues Much has been written about the differential diagnostic value of the character of the lesion In general however monolocular or unilocular character is of little differential value since lesions in mild cases may be unilocular as is true also of chickenpox and herpes In smallpox and vaccinia lesions in a given area of the skin usually are in the same stage of development in contrast to the pleomorphic eruption of chickenpox The most useful diagnostic procedures are the laboratory tests mentioned in connection with chickenpox Sometimes a biopsy of the skin may be of differential diagnostic value Vaccination for purposes of diagnosis should not be done By the time the result of the vaccination becomes apparent the disease usually could have been diagnosed clinically anyway If the disease is not vaccinia the patient is at risk of developing generalized vaccinia in connection with the skin eruption

The skin and mucous membranes are the principal areas of viral activity but there is also systemic involvement to include most of the organs One to three weeks after exposure there is usually sudden onset with fever, malaise chills headache and backache or pains in the extremities which may be very severe Vomiting is common and may continue for several days Symptoms tend to increase in severity During this period of one to five days some patients may have a transient diffuse, morbilliform, scarlatinal or petechial rash This probably results from viremia and localization of virus in the skin The temperature drops and the patient feels better when the true rash appears This is maculopapular and goes through a fairly characteristic course, becoming vesicular, pustular and finally forming crusts these crusts eventually fall off ten days to six weeks after the appearance of the eruption Mild cases with few lesions may escape the pustular stage On the mucous membranes shallow painful ulcers develop The fever tends to rise again with the appearance of the vesicles and more especially the pustules

There sometimes is leukopenia at the onset of the initial symptoms although a mononuclear leukocytosis may have developed during the incubation period A polymorphonuclear leukocytosis occurs during pustulation Thrombocytopenia is evidence of bone marrow involvement and is pronounced in the severely toxic or hemorrhagic type of case There usually is generalized lymphadenopathy, the liver and spleen are palpable and there is involvement of the kidneys is shown by albuminuria Pneumonitis is not uncommon and may be extensive and even fatal Fatal cases also show cloudy swelling and hemorrhages of the myocardium

The prognosis depends usually not so much on the skill of the practitioner as on the particular type of virus producing the disease and the reaction of the individual patient Some strains produce almost invariably the mild disease commonly called alastrim or variola minor In this instance, the eruption may be scanty, symptoms are extremely mild, and the case fatality rate 1 per cent or less In the more severe type of disease called variola major the symptoms tend to be in proportion to the extent of the eruption which may even become con

secondary bacterial infection which may be controlled by use of appropriate antibiotics and postvaccinal encephalitis which occurs rarely and usually not in more than one person out of every several hundred thousand vaccinated Treatment is discussed under rabies vaccine reactions

Generalized vaccinia occurs infrequently and may develop either in the absence of pre-existing skin lesions or in the eczematous individual or person with other types of skin involvement The disease is managed in the same manner as a mild case of smallpox

Because of the danger of this type of *reaction*, persons with eczema burns or other skin lesions should not be vaccinated if it is possible to avoid it They should not even be in the same environment with a freshly vaccinated individual The risk of danger of vaccination in pregnancy is nil

An occasional individual may develop a maculopapular rash not unlike that seen in German measles approximately a week to ten days after vaccination This is possibly a vascular response to viremia

Antibiotic therapy has no effect on the course of vaccination and will not prevent a successful take It is well to recall that false positive serologic reactions for syphilis frequently occur after vaccination and may persist for periods of weeks to six months Milkers nodules, the red itching papules occasionally seen on the hands of individuals who have been handling cattle are thought to be a type of vaccinia or cowpox Exact etiology of the disease is unknown Usually only one or few lesions are encountered which disappear spontaneously after several weeks The treatment is symptomatic.

Vaccinia

VACCINIA may be localized after vaccination or generalized, either following vaccination or by contact from others Vaccination commonly is given all persons exposed to smallpox or prophylactically to all individuals preferably during the first year of life either at birth or more usually from six to twelve months of age Since the duration of protection is approximately five years it is necessary to repeat vaccination at this interval throughout life Calf lymph vaccine commonly is used this is living virus which is highly thermosensitive and consequently may be readily inactivated if kept at room temperature for more than a few hours In the tropics or in areas where refrigeration is not possible virus which has been frozen and dried *in vacuo* may be used successfully

Vaccine usually is applied to the outer upper surface of the arm but can be given equally well in the axillary fold particularly the posterior axillary fold if it is desired to avoid a readily visible scar The legs should not be used as a site of vaccination since if secondary infection does develop it is more difficult to control in that area

The skin should be cleaned with ether or acetone never alcohol which might inactivate the virus A needle is held at an angle of 20° to 30° to the surface of the skin and the point applied to the skin surface ten to twenty times through a drop of vaccine on the skin within an area of 3 mm Blood should not be drawn Excess vaccine is wiped off Shields and dressing should not be used after vaccination because of danger of tetanus but a light gauze dressing may be applied to the sleeve over the lesion at the time of vesiculation The vaccinated individual should be warned not to scratch the area because of risk of transfer of infection to other parts of the body or to other individuals Several types of reaction may occur following vaccination There may be no take at all usually sooner or later everyone will get a take

It is not known why the occasional individual may be repeatedly nonreactive to vaccination The usual explanation that inactive virus was always used probably is not the final answer Passive immunity may be the reason for nonreacting infants of immune mothers There may be an immediate reaction in which a papule surrounded by a reddened area of erythema appears within twenty four to forty-eight hours The reaction occurs in persons previously sensitized to the virus and can be elicited with either virulent or inactivated virus A secondary infection at the site of vaccination may sometimes be mistaken for an immune reaction The vaccinoid or accelerated reaction appears in the partially immune person within three to five days with a papule and vesicle The height of the reaction is attained on the sixth or seventh day with a pustule which becomes crusted and leaves a scar The lesion differs from the typical take in the nonimmune individual only in the rapidity of its development In the typical take of the non immune or not previously vaccinated individual the papule appears within three to five days followed by a vesicle surrounded by erythema and induration which becomes pustular and gradually increases in size up to the ninth or tenth day There may be generalized symptoms of chills fever aching malaise, and local tenderness Usually the regional lymph nodes are enlarged and tender Eventually a scab forms which is shed after several weeks It is best to observe the vaccinated individual on the third and ninth day after giving the vaccination and to note the types of reactions on both occasions

Complications of vaccination include

Classification of Rickettsial Diseases

THE rickettsial diseases may be divided into five broad groups (1) the *typhus group* which includes epidemic (louse borne) typhus endemic (flea borne) typhus and *recrudescent epidemic typhus* (*Brill s disease*) (2) the *spotted fever group* which comprises Rocky Mountain spotted fever (eastern and western types) transmitted by the dog tick (*Dermacentor variabilis*) and the wood tick (*Dermacentor andersoni*) respectively (in addition boutonneuse fever Sao Paulo typhus of Brazil South African tick bite fever North Queensland tick typhus Russian[1] and Indian tick typhus are commonly included in this group) (3) the *tsutsugamushi group* which includes Japanese river fever, tropical typhus and scrub typhus of New Guinea Malaya Indo China Dutch East Indies and Australia in these diseases the larval form of a mite is the vector (*Trombicula akamushi* in Japan and New Guinea and *Trombicula deliensis* in New Guinea and Burma) (4) the *Q fever group, occurring in* Australia and the United States chiefly through contact with infected animals their products or excreta Outbreaks in Italy Greece and various laboratories have been described in which the respiratory route of infection has been suggested Ticks have been found infected in nature but their role in the transmission of the disease to man has not been evaluated (5) The most recently described group is *Rickettsialpox* whose vector is a mite (*Allodermanyssus sanguineus*) common to house mice

[1] *Recent studies on rickettsial strains from Siberian tick typhus indicate that they may by R prowa ekii* or epidemic typhus rather than rickettsiae of the spotted fever group

Diagnosis

SPECIFIC diagnostic confirmation of these diseases may be obtained through isolation of the rickettsiae by animal inoculation of blood or tissue In *Q fever* sputum spinal fluid and urine may also contain the causative agent Agglutination tests employing *Proteus* bacilli strains OX 19 OX 2 and OX K provide an aid but they usually do not become positive until the second week of illness These tests although reliable are not specific and do not permit differentiation among the various types of infection No proteus agglutinations develop in patients suffering from *Q fever* or *Rickettsialpox*

Specific antibodies develop in the sera of the patient which will agglutinate heavy suspensions of rickettsiae These agglutinations can be employed to differentiate among the various rickettsial diseases This test is most valuable when murine typhus is suspected in a patient who has previously received epidemic typhus vaccine Complement fixation in this situation may resemble the pattern seen in epidemic typhus but agglutinins in high titer for murine rickettsiae can be demonstrated

The *complement fixation* test employing washed rickettsial suspensions obtained from yolk sac or other special sources is a most valuable and definitive test Cross reactions do occur but these have been well characterized and when coupled with the clinical observations permit specific etiologic diagnosis The important differential serologic tests are summarized in Table 4

8. *Rickettsial Infections*

EMANUEL B SCHOENBACH

DURING the past fifteen years knowledge concerning the rickettsial diseases has expanded considerably With the aid of improved laboratory methods for isolation culture and serologic study the group has been separated into distinct clinical and epidemiologic entities This has permitted investigation on a more rational basis for control prevention and treatment

The causative agents rickettsiae are a group of micro-organisms which are frequently found in the tissues of insects and which under certain circumstances cause diseases in man They are small pleomorphic coccobacillary organisms which have never been cultivated on artificial media but which can be grown in tissue culture or the embryonated hen s egg When grown on tissue culture or seen in infected animal tissues many species of rickettsiae appear to be in the cytoplasm or nucleus In these characteristics the rickettsiae resemble the filterable viruses In size they are somewhat larger than most viruses and smaller than bacteria

The essential *lesion* caused by the rickettsiae is vascular Damage to the smaller blood vessels with endothelial proliferation thrombosis and perivascular round-cell infiltrations is the characteristic lesion and has been called the Fraenkel nodule These lesions are commonly found in the skin subcutaneous tissues and central nervous system They are also found in the heart liver kidneys and spleen

The rickettsiae invade the endothelial cells directly Although specific toxic products have been isolated which are lethal to experimental animals when injected intravenously there is no evidence that the pathologic changes observed in these diseases can be attributed to a soluble exotoxin elaborated by the rickettsiae The vascular lesions are clinically manifest as a characteristic rash consisting of an erythematous maculopapular eruption which may progress to hemorrhage and necrosis

The rickettsiae are dependent upon the metabolic activity of the host cell for survival and proliferation Early studies by Zinsser and Schoenbach showed that growth of rickettsiae in tissue culture occurred when the respiration of the cells was at a minimum Subsequent studies have shown that cells poisoned with cyanide or carbon monoxide still permit rickettsial growth and that riboflavin-deficient animals were more susceptible to infection Conversely stimulation of cellular metabolism appeared to exert a deleterious effect on rickettsial proliferation To date none of the chemotherapeutic agents which have been employed successfully possesses direct antirickettsial activity It would appear that these agents exert their therapeutic properties on the metabolism of the host cell so that proliferation of the rickettsiae is suppressed

containing pyrethrum or DDT (*10 per cent*) under epidemic conditions in North Africa Naples and the German concentration camps (1943–1945)

CLINICAL COURSE

The onset of typhus is usually abrupt with malaise, severe headache chilly sensations and fever The fever is maintained for twelve to twenty days A *maculopapular rash* appears between the third and sixth day of illness, first on the abdomen and lower chest, thence extending rapidly to involve the extremities The palms, soles and face are usually spared even in severe cases Although initially this rash is erythematous it may become hemorrhagic in severe cases

Complications

The most common complications are marked hypotension with renal insufficiency pneumonia encephalitis cutaneous gangrene with secondary bacterial infection parotitis and otitis media The mortality of the untreated disease varies in different epidemics and with the age of the patient In general, a gross fatality rate of 10 to 40 per cent has been observed The disease is mild in children and severe among adults over 40 years of age

SUPPORTIVE THERAPY

Nursing is particularly important in this disease where somnolence and delirium are so common Bed rest during the febrile period is required Constant supervision is necessary to keep the delirious patient from doing himself harm Stuporous patients must be turned frequently to minimize the incidence of hypostatic pneumonia Skin infections and bed sores can be prevented through the use of daily baths air cushions to support pressure points and generous applications of talcum powder Sponges for high fever are helpful Mouth washes and oral hygiene are important to prevent parotitis.

Diet A daily intake of approximately 3000 cc of fluids should be encouraged so that a urinary output of at least 1500 cc is obtained Fluids should be given orally at frequent intervals and supplemented by intravenous fluid or gavage when necessary A high calorie, high protein high vitamin liquid diet is best tolerated Except when edema or evidence of congestive heart failure is present sodium chloride in doses of 5–10 Gm per day is desirable If the patient is critically ill the state of the vascular system including frequent determinations of blood pressure, should be assiduously observed Whole blood plasma albumin, and isotonic saline or dextrose infusions at the first appearance of hypotension may prevent shock and impairment of renal function

The use of antipyretic drugs which cause febrile fluctuations only leads to further exhaustion of the patient Cough and headache are partially relieved by codeine Chloral hydrate and paraldehyde may be used for control of delirium Barbiturates and morphine appear to exert little beneficial effect and may be harmful Digitalis preparations although of questionable value have been used when heart failure is present Oxygen has similarly been used for the alleviation of cyanosis Hemoglobin determinations urinalysis and blood nonprotein nitrogen or blood urea nitrogen levels are important in determining fluid requirements

All patients ill with epidemic typhus should be *deloused* promptly Clothes may be disinfested with heat The patient is bathed with soap and water or *1 per cent* cresol solution He and his bedding are dusted with DDT powder at weekly intervals Personnel exposed to typhus patients should be immunized with specific vaccine and DDT dusting powder utilized at weekly intervals

During the second World War a vaccine prepared from the yolk sac of infected embryonated hen s eggs was effective in the

TABLE 4 DIAGNOSIS OF RICKETTSIAL DISEASES

Rickettsial disease	Etiologic agent	Common vector	Weil-Felix Proteus antigen			Complement fixation test antigen					
			OX 2	OX 19	OX K	R. prowazeki	R. mooseri	R. rickettsii	R. akari	R. orientalis	C. burneti
Epidemic louse borne typhus (classic)	*R. prowazeki*	body louse	+	++	−	++*	+*	−	−	−	−
Endemic flea borne typhus (murine)	*R. mooseri*	rat flea	+	++	−	+*	++*	−	−	−	−
Recrudescent epidemic typhus (Brill's disease)	*R. prowazeki*	none	+	++	−	++*	+*	−	−	−	−
Rocky Mountain spotted fever	*R. rickettsii*	Eastern dog tick western wood tick	++	++	−	−	−	++	+	−	−
Tsutsugamushi disease (scrub typhus)	*R. orientalis*	larvae of mite	−	+	++	−	−	−	−	±	−
Q fever	*C. burneti*	cattle(?) milk	−	−	−	−	−	−	−	−	++
Rickettsialpox	*R. akari*	mite of house mouse	−	−	−	−	−	+	++	−	−

− Negative
++ Positive in high titers
+ May be positive in low titers
= Not available for standard diagnostic procedure
* In previously infected and vaccinated individuals dual rickettsial agglutinations may aid in differential diagnosis

Epidemic Typhus

EPIDEMIC typhus has been associated for the past four hundred years with mass misery military operations and pestilence During the period following the first World War (1918 1922) approximately 30 million cases were recorded in Russia 3 million died As recently as 1942 and 1943 severe epidemics occurred in North Africa Naples and in some of the German concentration camps

The *body louse* is the most important vector for this disease and control of louse infestation will eliminate epidemic typhus The validity of this approach has been dramatically demonstrated through the use of mass dusting with insecticide powders

responsive may be treated with aureomycin administered *parenterally* The antibiotic is available to hospitals only in vials containing 0 1 or 0 5 Gm of aureomycin hydrochloride together with sodium glycinate as a buffer A minimum of 10 cc of distilled water or 5 per cent glucose in distilled water for each 0 1 Gm of aureomycin are employed as diluent However it is usually more satisfactory to employ 20–50 cc diluent for each 0 1 Gm of aureomycin The preparation of these intravenous solutions requires some care to avoid particulate suspension Ten cubic centimeters of diluent per 0 1 Gm of drug are introduced rapidly into the vial with constant agitation When the drug has dissolved the solution may be withdrawn and further diluted Some preparations of aureomycin hydrochloride for intravenous use are unbuffered A special diluent containing leucin and sodium hydroxide which is packaged with these vials must be employed Five cubic centimeters of this diluent are employed to dissolve 0 1 Gm of aureomycin These buffered solutions of aureomycin lose antibiotic activity on standing and should therefore be used not more than several hours after preparation

The *intravenous* dosage of aureomycin is approximately 5 0–10 0 mg per kg body weight An individual dose of 0 5 Gm should not be exceeded It may be repeated two to three times a day Detectable blood levels persist for approximately eight hours after each administration Untoward manifestations such as flushing feeling of oppression in the chest or suboccipital pain may be avoided by administration at a rate not to exceed 50 mg of aureomycin per minute

The drug is quite irritating locally and care should be employed to avoid extravascular extravasation Chemical phlebitis may be minimized by diluting the drug beyond the maximum recommended concentration and by using different veins and sites for intravenous administration The intravenous route may be employed as a substitute or a supplement for oral administration of aureomycin The oral route is preferred and should be resorted to as soon as possible Intramuscular administration of aureomycin is too painful and not advised

The *rectal administration* of aureomycin may be employed for several doses but it *cannot be maintained because of local* irritation Suppositories may be formed of 0 25 Gm of aureomycin in a cocoa butter base The dosage is the same as that described for the oral route but absorption is erratic.

The oral use of aureomycin is not contraindicated in the presence of renal insufficiency and the dosage does not require adjustment

Chloramphenicol The clinical response to chloramphenicol in typhus fever is almost identical to that observed with aureomycin The antibacterial spectrum of chloramphenicol is similar to that of aureomycin, although it appears to be more effective in gram negative bacillary infections and less active in the gram positive coccal group Nausea and vomiting are not as frequently encountered as with aureomycin or terramycin

The *dosage schedule* of chloramphenicol recommended for the treatment of typhus fever is an initial oral loading or priming dose of 20 mg per kg body weight at hourly intervals for a total of three doses The oral drug is then continued on a schedule of 10–20 mg per kg body weight (0 5 Gm for a 60 kg adult) every four hours day and night The patient will usually become afebrile after forty eight to seventy two hours and the daily dosage may then be diminished by extending the interval to six or eight hours between administrations The antibiotic can usually be discontinued after the sixth day of therapy

For those patients who cannot swallow capsules the chloramphenicol may be

prevention of epidemic typhus One cubic centimeter of this vaccine can be administered subcutaneously for prophylaxis at weekly intervals for three doses A booster injection of 1 cc should be given when an epidemic or intimate exposure occurs more than three months after the primary series or last booster injection The prophylactic value of the therapeutically active antibiotics has not been evaluated at present

SPECIFIC THERAPY

Chemotherapy

Only during the past seven years has specific therapy been available for the treatment of rickettsial diseases In 1942, *p* amino benzoic acid (PABA) was shown to protect animals experimentally infected with the rickettsiae of typhus fever In 1943 this drug was employed for the therapy of clinical cases A significant reduction in mortality from the disease attended the use of PABA when treatment was begun before the eighth day of illness

In 1948, *aureomycin* and *chloramphenicol* and in 1950 *terramycin* became available for the treatment of rickettsial infections * These chemotherapeutic agents have been shown to protect animals experimentally infected with the rickettsiae of epidemic and endemic typhus spotted fever scrub typhus Q fever, and rickettsialpox Aureomycin and terramycin have been shown to protect experimental animals from the toxic properties of nonviable rickettsiae injected intravenously Trial in clinical infections has been limited but even the short experience indicates that they are by far the agents of choice for the treatment of rickettsial diseases The toxicity of these antibiotic agents is low and no hepatotoxic nephrotoxic or other serious untoward reactions have been noted.

Side-effects Nausea with occasional emesis has been noted with these antibiotics Loose stools which may become watery are some of the annoying complications of antibiotic therapy The secondary development of monilia with attendant infection or sensitivity response is a more distressing complication The inflammation of the mucous membranes of the mouth tongue vagina, anus, and rectum is probably a manifestation of antibacterial action of the antibiotics with secondary monilial proliferation Fortunately these complications are only seen in patients receiving the antibiotic for extended periods of time Hypersensitivity reactions to aureomycin, chloramphenicol, and terramycin are quite uncommon Hematologic complications have only been observed with chloramphenicol With the latter antibiotic, erytheroid and myeloid maturation arrest has been noted in the bone marrow accompanied by leukopenia, granulocytopenia, and anemia in the peripheral blood Occasional patients have developed an aplastic anemia

Aureomycin The oral dosage of aureomycin recommended for the therapy of epidemic typhus is approximately 5–10 mg per Kg body weight (0 5 Gm for a 60 Kg adult) every four hours day and night The dosage in children is somewhat greater proportionately so that a daily dosage of 50–60 mg per Kg of body weight is attained

When the patient becomes afebrile and remains so for a twenty four hour period, the daily dosage may be reduced by changing to a six or eight hour schedule The patient is generally afebrile after forty-eight hours of treatment Aureomycin therapy for a total period of six days is usually adequate For children who cannot swallow capsules the drug may be dissolved or suspended in chocolate syrup or honey Comatose patients may require administration of the antibiotic by gavage The use of aluminum hydroxide preparations to minimize gastrointestinal disturbances is not advised

Patients who are extremely ill or un

* See also Chapter 4

PABA has been employed in an initial oral dose of 0.1 Gm per kg body weight (1-8 Gm) followed by 25 mg per kg (1-3 Gm) every two hours until the fever has subsided and the patient is afebrile for at least forty-eight hours A blood level of 20-30 mg per 100 cc. should be maintained Concentrations of PABA in the blood should be kept below 50 mg per 100 cc. When possible frequent determination of blood concentration should be made during the first forty-eight hours When the levels have stabilized daily blood levels are indicated

The chemically pure acid or sodium salt of PABA is tolerated by mouth Equivalent weights of sodium bicarbonate administered as a 5 per cent solution with the PABA, is used in order to maintain an alkaline urine Solutions of sodium PABA may be administered by nasal tube when there is difficulty in swallowing An intravenous preparation of sodium PABA is available

PABA may produce *toxic reactions* A fall in the total white blood cell count below 3000 per cu mm or a granulocytopenia of less than 25 per cent are indications for discontinuing therapy Liver and kidney damage have been observed at post mortem examination of several patients treated with PABA for diseases other than those caused by rickettsiae It is advisable therefore, to perform frequent tests of hepatic function blood nonprotein nitrogen, and carbon dioxide blood content in addition to daily white cell counts and PABA blood levels The drug should be discontinued if PABA crystals appear in the urine However, renal insufficiency prior to treatment is no contraindication to therapy provided frequent determinations of blood PABA concentrations with careful adjustment of dosage are possible There are few indications for the use of PABA at the present time

Treatment of Complications

Penicillin and streptomycin are occasionally useful in the treatment of the secondary infections accompanying typhus They show some protection of experimental animals but have not been demonstrated to have clinical value in rickettsial disease Sulfonamide compounds appear to be contraindicated They neutralize the action of PABA and clinical trials have shown them to be ineffective and possibly harmful

Endemic (Murine, Flea-Borne) Typhus

IN 1926 Dr Kenneth Maxcy first recognized the existence of a form of typhus fever unassociated with louse infestation and most commonly seen among individuals employed as food handlers This form of typhus has been shown to be due to a rickettsia transmitted from rats to man by the rat flea The disease is worldwide in its distribution In the United States, the infection is most common in the southeastern states

Endemic typhus has a comparatively low mortality (approximately 5 per cent) but the clinical course of the disease may be quite severe Control of this disease is dependent on elimination of contact with rats

Clinically the disease resembles a somewhat milder form of epidemic typhus The *rash* appears on the abdomen and lower chest and spreads centrifugally to the extremities, but usually does not become hemorrhagic and is of shorter duration than in epidemic typhus Fever is sustained

suspended in syrup or given by gavage The drug is quite bitter and children cannot easily be induced to take these fluid preparations by mouth

Chloramphenicol palmitate is a tasteless preparation which may also be employed It is available as a suspension in which 5 cc contains 0 125 Gm of the chloramphenicol base Blood levels should be measured when this preparation is prescribed as the lipase activity necessary to release the chloramphenicol may be deficient in severely ill children

Chloramphenicol is well tolerated and readily absorbed when instilled into the *rectum* Suppositories containing 0 25–0 5 Gm of chloramphenicol can be prepared and the dosage required is similar to that recommended for the oral route

No parenteral forms of chloramphenicol are available at present for clinical use However investigations have been conducted with a microcrystalline chloramphenicol which can be suspended in saline and administered intramuscularly This preparation is well tolerated locally is non painful results in satisfactory blood levels which are maintained for twelve hours and has been effective therapeutically A suspension of chloramphenicol containing 2 Gm per 5 cc of saline can be prepared The daily dosage of 60–100 mg per kg body weight can be divided into two or three parts and administered at appropriate intervals Other parenteral preparations are at present being investigated

In the presence of *renal insufficiency* the dosage of chloramphenicol should be carefully regulated as the blood level of drug may rise to levels considered harmful (over 200 μg per cc of serum) Chloramphenicol is conjugated in the liver and excreted in the urine The blood level of biologically active chloramphenicol should be measured

Terramycin The antibacterial activity of terramycin closely resembles that of aureomycin For the treatment of rickettsial infections the *oral dosage* of terramycin advocated at present is 10–15 mg per kg body weight every four hours day and night The larger doses are employed for children The febrile response is somewhat delayed so that this dosage should be maintained for three to five days The total daily dose may then be reduced by lengthening the interval to six or eight hours Therapy is recommended for at least four days after the patient has become and remained afebrile Patients who cannot swallow capsules may receive terramycin in solution as a syrup as the elixir (terrabon 5 cc equals 0 25 Gm) an oral suspension in a flavored vehicle (5 cc equals 0 25 Gm) or by gavage

An *intravenous* preparation of terramycin hydrochloride is available for hospital use in vials containing 0 25 Gm of the antibiotic Sodium glycinate has been added to the crystalline terramycin so that upon dilution with 100 cc sterile 5 per cent glucose in distilled water or isotonic solution of sodium chloride the resulting solution will have a *p*H of approximately 9 0 The solution is quite stable and will maintain its antibiotic activity for seventy two hours after preparation if stored at 4° to 6° C

The terramycin hydrochloride solution should be administered intravenously only A daily dose of 20 mg per kg body weight or a total of 1 Gm should not be exceeded at present It may be divided into two or three parts and administered at twelve- or eight hour intervals The rate of administration should not exceed 50 mg per minute The oral route is preferred and should be instituted as soon as possible

Other Chemotherapeutic Agents *p*-Aminobenzoic acid (PABA) has been employed in the therapy of rickettsial infections Because of its therapeutic limitations and toxic properties it has been supplanted by the newer antibiotics aureomycin chloramphenicol and terramycin

northwestern parts of the United States In addition the group includes South African Tick fever boutonneuse fever Sao Paulo typhus of Brazil and other South American countries and North Queensland tick typhus

CLINICAL COURSE

In many of its general aspects Rocky Mountain spotted fever resembles typhus fever The chief differential clinical characteristics of the spotted fever group are the time of appearance and mode of spread of the eruption The site of tick bite may be evident and associated with local adenopathy *The rash appears on the third to* fourth day of illness usually about the ankles and wrists, and spreads centripetally to involve the face chest and abdomen The palms and soles may be involved In severe cases this maculopapular erythematous eruption may become deep red or purple and sometimes necrotic The fever tends to be remittent in type and usually terminates by lysis during the third week of illness

Complications are frequent and myocarditis, parotitis pneumonia and encephalitis are seen in one fourth of hospitalized patients *The mortality varies in different* regions and among different age groups In children the mortality of the untreated disease is approximately 10 per cent while in adults over 40 years of age the mortality rate may be over 40 per cent In the Bitter Root Valley Montana the mortality among children is 37 per cent and among adults 80 per cent

TREATMENT

p Aminobenzoic acid was first used for the treatment of Rocky Mountain spotted fever in 1946 The mortality and complications were reduced In severe cases results were equivocal and when treatment was begun after the seventh day the drug did not appear to influence the course of the disease

In 1948, aureomycin and chloramphenicol were introduced with excellent results Infants, children, and adults became afebrile within forty eight to seventy two hours No complications or deaths were noted in these treated series Terramycin has also been found to exert a beneficial effect although fever appears to persist for a longer period than with aureomycin or chloramphenicol

The schedule for administration of these antibiotics is the same as that for epidemic typhus No relapse has been observed even when the total duration of treatment has been only four days Supportive therapy is the same as that used in typhus

PREVENTIVE THERAPY

In regions where ticks are abundant careful inspection of the skin and head each evening is advisable for prophylaxis Ticks should be removed with a forceps to minimize infection through the hands* Dogs should also be carefully examined for ticks DDT dusting has not been effectual for controlling the tick population or for the removal of ticks attached to one s person A vaccine prepared from infected yolk sacs of embryonated hen s eggs has been found most effective in children Three injections of 1 cc of the vaccine at weekly intervals after appropriate inquiry as to hypersensitivity to egg protein is recommended in highly endemic areas It should be given in the late winter in the west or early spring in the east

* See also Chapter 9

and in the uncomplicated case generally lasts ten to fourteen days Defervescence is usually by lysis Complications are less frequent than in epidemic typhus Approximately 5000 cases have been reported each year in the United States

TREATMENT

The treatment of endemic typhus is the same as that for epidemic typhus Aureomycin chloramphenicol, or terramycin appear to be the drugs of choice

Brill's Disease

A UNIQUE form of typhus which occurred among immigrants from endemic typhus areas of southeastern Europe the Baltic countries and Ireland has been observed in New York City Boston, Philadelphia and Baltimore Originally termed Brill's disease it was often confused with typhoid fever and endemic murine typhus Zinsser's observation that this disease probably represented a recrudescence of epidemic typhus fever has been substantiated by subsequent laboratory studies The strains of rickettsiae isolated from these cases have been of the epidemic type and complement fixation tests also indicate that the infection is of the epidemic variety

Clinically the disease simulates a mild form of typhus fever Often a history of previous typhus infection may be elicited There is practically no mortality although the patient may appear to be quite ill with severe headache somnolence and the characteristic maculopapular eruption The disease usually terminates by crisis on the tenth to the fourteenth day and complications are rare

TREATMENT

The course of the disease may be materially shortened with specific therapy provided the diagnosis can be made sufficiently early Aureomycin by mouth has been successfully employed the dosage being that for epidemic typhus

Rocky Mountain Spotted Fever (Eastern and Western Types)

THIS disease was known in Idaho as early as 1873 The first experimental transmission of a rickettsial disease was achieved by H T Ricketts in 1906 with Rocky Mountain spotted fever He showed that the wood tick (*Dermacentor andersoni*) was the important human vector and that the rickettsiae were transmitted by ticks via the ova to successive generations His observations were confirmed and extended by S B Wolbach

Rocky Mountain spotted fever when first identified was thought to be limited to the northwest mountain region of the United States Spencer and Maxcy in 1930 noted infected individuals in rural areas of the mid Atlantic states whose disease simulated Rocky Mountain spotted fever A history of tick bite was obtained from many of these patients This disease was identified as Rocky Mountain spotted fever (eastern type) by Rumreich, Dyer, and Badger in 1931 It is transmitted by the dog tick (*Dermacentor variabilis*) There is no valid reason to separate the disease as it occurs in the southern eastern or the

Q-Fever

Q FEVER was first recognized in 1935, among slaughterhouse workers in Australia and the rickettsial etiology was established by F M Burnet A similar rickettsia was isolated from ticks in Colorado by Herald R Cox Subsequently cases have been found in various regions of the United States, Italy, Switzerland, Greece and Panama Different species of ticks have been found infected, but their relationship to the disease in man is still obscure Bandicoots and cattle have been found to harbor the rickettsiae and epidemics have been associated with contact with meat, hides, or ingestion of milk or milk products Other explosive epidemics have been reported in which a respiratory mode of transmission has been suggested Epidemics in laboratories in which Q fever rickettsiae are handled have also been fairly common

CLINICAL COURSE

Q fever is usually sudden in onset after an incubation period of two to four weeks *Headache, fever, muscle pains, and anorexia* are the chief symptoms The febrile period is variable It is shorter in younger age groups and may be prolonged to several weeks among older individuals The fever is swinging in type No rash is associated with this disease Nausea and emesis may be severe and headache is prominent A cough develops toward the end of the first week and chest pain may also be noted In some epidemics the disease simulated primary atypical pneumonia Pulmonary involvement may be elicited by physical and roentgen examination among the majority of patients

Complications are rare but the course of the disease is often hectic with pronounced weight loss and weakness *Mortality* has not exceeded 4 per cent Many cases of mild atypical or inapparent infections have been disclosed by serologic and epidemiologic surveys

TREATMENT

Treatment of this disease was limited to nonspecific supportive therapy until 1948 Aureomycin has been used with good results in the acute disease The dosage of aureomycin required is greater than in the other rickettsial diseases and relapses—which have responded to a second course of treatment—are frequently observed The recommended dosage is 4–6 Gm (50–100 mg per kg body weight) during the first twenty four hours followed by 3–4 Gm daily (50–60 mg per kg body weight) divided into six aliquots each day for a minimum of five days Subsequent therapy with smaller doses (20–30 mg per kg body weight) is maintained for approximately two weeks

Parenteral Aureomycin Some cases of *Q fever which have not responded to oral* therapy have shown a prompt remission when oral therapy was supplemented by parenteral aureomycin The intravenous injection of 0 1–0 3 Gm of aureomycin is given twice daily for several days in addition to the oral therapy Nausea and vomiting have been prominent with these combined doses of aureomycin However, these symptoms were frequently observed among many of the patients before treatment was instituted *Chloramphenicol* appears to be *equally effective* but has not been critically evaluated in this disease *Terramycin* which is more active than aureomycin in animals has not demonstrated any superiority on preliminary clinical trial

Tsutsugamushi Disease (Scrub Typhus)

TSUTSUGAMUSHI disease long has been recognized in Japan Infection has been associated with the red mite (*Trombicula akamushi*) During the second World War approximately 7000 cases were reported among American troops in the South Pacific with a gross fatality rate of 4 per cent The mortality among older individuals was distinctly higher Extensive study has revealed that the disease occurs in Indo-China, Malay States, the East Indies New Guinea, and the coast of Australia The disease is commonly referred to as scrub typhus because infection is associated with exposure to virginal kunai grass and scrub

CLINICAL COURSE

The disease usually begins after an incubation period of one to two weeks with abrupt onset of headache chills and fever A local eschar consisting of a necrotic ulcer at the site of the mite bite is characteristic The fever increases during the first week and is associated with a relative bradycardia A characteristic macular rash appears on the trunk between the fifth and eighth day and extends to involve the extremities This rash may persist for ten days or may be evanescent and be present for only a few hours Generalized lymphadenopathy and splenomegaly are common However the diagnostic significance of the latter is materially decreased due to concomitant malarial infection in many of these areas The fever is maintained for two weeks after the fastigium is reached and then falls slowly by lysis The common complications are myocarditis, pneumonia, and encephalitis

TREATMENT

p Aminobenzoic acid has been used for the treatment of scrub typhus However, chloramphenicol, aureomycin and terramycin appear to be more effective chemotherapeutic agents The dosage schedule recommended for the treatment of epidemic typhus is employed Patients usually become afebrile within two days

Preventive Therapy

At present there is no effective vaccine for the prevention of tsutsugamushi disease Kunai grass and scrub should be cut and burned before establishment of camp sites The clothing should be impregnated with miticides (dimethyl and dibutyl phthalates)

Studies on the use of the antibiotics as prophylactic agents have shown that treatment during or immediately following the period of exposure is only suppressive Illness and rickettsemia will occur one to two weeks later Four to six courses of antibiotic at intervals of eight to twelve days may be required to prevent manifest clinical symptoms Aureomycin (2 Gm) or chloramphenicol (3 Gm) daily for two to three days given at these intervals has been shown to be effective The optimal dosage and schedule of these antibiotics is still being explored for the prevention of scrub typhus among personnel exposed in highly endemic areas.

with morning remission, persists for approximately one week. The eruption appears on the third to fifth day of fever and is distributed on the abdomen, back, and upper portions of all extremities. The rash begins as a maculopapular discrete eruption which rapidly becomes vesicular, resembling varicella. It persists for five to ten days and then dries to form crusts which desquamate without scarring of the underlying tissue. There are no reported complications.

TREATMENT

Infection with *R. akari* rapidly responds to aureomycin, chloramphenicol, or terramycin, and it would appear that these antibiotics shorten the duration of this mild disease. A dosage schedule similar to that for typhus fever may be employed.

Control of mice through careful storage of foodstuffs and disposal of garbage should prevent contact and resultant infection. No prophylactic vaccine has been evaluated.

PREVENTIVE THERAPY

No reliable data with respect to vaccine prophylaxis are available. Quarantine of patients is not deemed necessary but careful disposal of sputum and excreta are recommended. Infection through the ingestion of contaminated milk is an important problem. The Q fever rickettsiae are unable to withstand the usual pasteurization processes when these are carefully performed. Butter has been shown to be infectious even after refrigeration for more than forty days.

No satisfactory prophylaxis for those engaged in the processing of meat or cattle products has yet been devised.

Rickettsialpox

THIS rickettsial disease has only recently been described in the environs of New York City (1946) and in Boston, Massachusetts in 1950. The causative rickettsia (*R. akari*) has been isolated from mites (*Alloderma nyssus sanguineous*) harbored on house mice and from the blood of patients. Because of its serologic behaviour some investigators classify this rickettsia among the spotted fever group. Clinically the absence of a Weil-Felix reaction in the sera of patients, the transmission by a mite, and the vesicular eruption would warrant its separation at present.

CLINICAL CHARACTERISTICS

Rickettsialpox is a relatively mild disease with no known mortality or residuae. It is characterized by sudden onset with headache, backache, fever, chills, and sweating. At the site of the mite bite, a vesicle develops which dries and forms a black eschar. This lesion usually appears one week before the febrile period. The fever,

TABLE 5. TREATMENT OF RICKETTSIAL DISEASES

Rickettsial disease	*Mortality of untreated disease* (%)	*Duration of fever in untreated disease* (days)	*Specific therapeutic agents*		
			Aureomycin	Chloramphenicol	Terramycin
Epidemic louse-borne typhus (classic)	10–40	12–20	A	A	C & D
Endemic flea borne typhus (murine)	5	10–14	A	A	B
Recrudescent epidemic typhus (Brill's disease)	0–10	10–14	A	D	D
Rocky Mountain spotted fever	10–80	14–21	A	A	B
Tsutsugamushi disease (scrub thyphus)	4–20	14–21	A	A	B
Q fever	4	7–21	A	C & D	C & D
Rickettsialpox	0	5–10	A	A	A

A. Agent of choice
B. Effective in the disease
C. Effective in experimental animals
D. Probably active but not adequately evaluated clinically

TABLE 6 OUTLINE OF PARASITIC INFECTIONS OR INFESTATIONS

Infection or infestation	*Etiologic agent*
PROTOZOAN INFECTIONS (protozoiasis)	
Amebiasis	*Endamoeba histolytica*
Intestinal flagellosis, including giardiasis	*Trichomonas hominis, Chilomastix mesnili, Giardia lamblia*
Trichomonas vaginitis	*Trichomonas vaginalis*
Balantidiasis	*Balantidium coli*
Coccidiosis	*Isospora hominis*
Malaria	*Plasmodium vivax, P malariae, P falciparum, P ovale*
Trypanosomiasis	*Trypanosoma gambiense, T rhodesiense, T cruzi*
Leishmaniasis	*Leishmania tropica, L brasiliensis, L donovani*
Toxoplasmosis	*Toxoplasma gondii*
HELMINTHIC INFECTIONS (helminthiasis)	
A ROUNDWORM INFECTIONS (NEMATODIASIS)	
Ascariasis	*Ascaris lumbricoides*
Trichocephaliasis	*Trichocephalus trichiurus (Trichuris trichiura)*
Hookworm infection	*Necator americanus, Ancylostoma duodenale*
Creeping eruption	*Ancylostoma braziliense*
Strongyloidiasis	*Strongyloides stercoralis*
Oxyuriasis	*Enterobius vermicularis*
Trichinosis	*Trichinella spiralis*
Filariasis	*Wuchereria bancrofti, W malayi, Onchocerca volvulus Loa loa*
Dracunculosis	*Dracunculus medinensis*
B TAPEWORM INFECTIONS (CESTODIASIS)	
Taenia infections	*Taenia saginata, T solium*
Cysticercosis	Cysticercus of *T solium*
Hydatid cyst	Hydatid larva of *Echinococcus granulosus*
Diphyllobothrium infection	*Diphyllobothrium latum*
Hymenolepis infections	*Hymenolepis nana H diminuta*
Dog tapeworm infection	*Dipylidium caninum*
Sparganosis	*Sparganum* spp
C TREMATODE ("FLUKE") INFECTIONS (TREMATODIASIS)	
Intestinal, hepatic and pulmonary trematodiasis	*Fasciolopsis buski*, Echinostomes, *Heterophyes et al, Fasciola hepatica, Clonorchis sinensis, Opisthorchis felineus, Paragonimus westermani*
Schistosomiasis	*Schistosoma japonicum, S mansoni, S haematobium*
D LEECH INFESTATIONS (HIRUDINIASIS)	*Limnatis nilotica, Haemadipsa* spp, *et al*
ARTHROPOD INFESTATIONS	
Pediculosis and flea infestation	*Pediculus corporis, P capitis, Phthirius pubis Tunga penetrans*
Mite infestation	*Sarcoptes scabiei, Demodex folliculorum, Liponyssus bacoti, Trombicula* spp
Tick infestation	Many species of ticks
Myiasis	Many species of flies
Spider and scorpion venenation	*Latrodectus mactans et al, Centruroides* spp *et al*
Bee sting	*Apus apus et al*
VENENATION DUE TO FISHES AND REPTILES	
Fish venenation	Several species of fishes
Lizard and snake venenation	Gila monsters, many species of front fanged snakes

ratory technics *microscopic examination of the stool* is the most important In formed feces the cystic stage is present, in loose or diarrheic stools the active trophozoite stage is recovered, particularly in small flecks of blood and mucus The stool should be fresh Liquid specimens are examined by direct film technic, formed stools are examined both by direct film and by zinc sulfate concentration Three stools, passed two or three days apart, must be examined before there is an eighty per cent assurance that the patient is free of infection Saline purges or high isotonic salt enemas

9. Parasitic Infections

ERNEST CARROLL FAUST

THE animal parasites of man include four major categories Protozoa or one celled organisms Helminths or parasitic worms Arthropods (including insects ticks mites spiders and scorpions) and Poisonous Fishes and Reptiles The Protozoa and Helminths (exclusive of the Leeches) are parasites which have an established relationship with the organs or tissues of the body Some of the Arthropods also invade the tissues (scabic mites and myiasis producing flies) but the majority which harm man are blood sucking or venenating forms which are only temporarily attached to the skin Many of this latter group are primarily important as transmitters of pathogenic bacteria viruses rickettsias spirochetes protozoa and helminths Some fishes a few lizards and many species of snakes introduce venom into the skin through spines teeth or specialized fangs

Table 6 presents an outline of parasitic infections for the purpose of orientation

Protozoan Infections (Protozoiasis)

AMEBIASIS

Amebiasis is infection with *Endamoeba histolytica* the one ameba pathogenic to man This infection is world wide and hyperendemic in most tropical areas It is acquired by mouth in the cystic stage from water food filth flies or direct contact with persons or objects contaminated by the cysts Although it is conceivable that this organism may propagate for several generations solely in the lumen of the large bowel it is actually a tissue invader the author has never found any strain of *E histolytica* without tissue invading capacity Typically entry is made by lysis into the intestinal mucosa at individual pinpoint sites The lesion consists of several to many amebas in the midst of necrosing tissue and is usually without any definite evidence of cellular infiltration unless bacteria enter the ulcer Damage may be confined to the mucosal layer although penetration frequently extends to the submucosa and at times into the muscular coats with the production of an enlarged base which involves more tissue destruction than the superficial appearance would suggest.

Diagnosis

Amebiasis may be suspected on clinical grounds but it can be diagnosed with certainty only by one or more of several labo-

to seven days In some patients it produces hypermotility of the colon with profuse diarrhea Therefore, it is contraindicated in patients already suffering from severe diarrhea and dehydration, *unless tincture* of opium is prescribed concomitantly to control the diarrhea An alternative in these cases, and regarded by many physicians as the drug of choice is *diodoquin* (5-7-diiodo 8 quinolinol), *which is admin*istered as 3 or 4 0 2 Gm enteric coated tablets three times daily with meals for twenty days *Vioform* (5 chloro 7 iodo 8 quinolinol) probably is equally effective when administered orally 1 0 25 Gm tablet or gelatin capsule of the powder is taken three times daily at mealtime for ten to twenty days However, its use in the United States has been limited

Carbarsone Although several arsenicals *have been screened pharmacologically and* therapeutically for antiamebic activity, carbarsone is the only one used routinely Carbarsone (*p* ureidobenzenearsonic acid) is administered as 1 0 25 Gm tablet or gelatin capsule, twice daily with meals for ten days It cures about 90 per cent of patients If the patient develops dermatitis or other signs or arsenic intolerance, treatment with carbarsone must be stopped and an iodoxy quinoline drug substituted

Milibis Milibis (bismuth glycolylar sanilate) a new synthetic arsenical, has been found to be very valuable in the treatment of intestinal amebiasis well within clinical tolerance Recommended dosage consists of two 0 25 Gm tablets taken by mouth three times daily for eight days or one 0 25 Gm tablet taken by mouth three times daily for twenty to thirty days In combination with chloroquine milibis has considerable pro*phylactic value*

In chronic amebic colitis with bacterial involvement of the ulcerated intestine the administration of sulfonamides or penicillin may be helpful in clearing up the involved areas preparatory to antiamebic therapy

In summary, antiamebic drugs presently available are not invariably curative Eme*tine hydrochloride must be administered* cautiously It is the only thoroughly tested drug for extraintestinal amebiasis its use in intestinal infection should be limited to two or three daily administrations for *symptomatic relief The author prefers the* hydroxyquinolines to carbarsone because of lesser potential reaction Newer drugs such as atabrine, chloroquine aureomycin bacitracin, terramycin and several arsenical compounds have not had sufficient clinical trial to assess their relative amebicidal usefulness one or more show definite promise The antibiotics are given in doses of 0 5 Gm every six hours for ten days

Since Endamoeba coli, Endolimax nana Iodamoeba bütschlii, and *Dientamoeba fragilis* have not been demonstrated to be pathogenic, their presence in the human intestinal tract does not require chemotherapeutic consideration

Control

The control of amebiasis is dependent on safe water supplies and sewage disposal clean food elimination of filth fly breeding and better personal hygiene

INTESTINAL FLAGELLOSIS

The three flagellate protozoa which are common parasites of the human intestinal tract are *Trichomonas hominis, Chilomastix mesnili*, and *Giardia lamblia* There is no substantial evidence that the former two are, in themselves pathogenic *Giardia lamblia* lives in the intestinal crypts most frequently at the duodenal level occasionally it invades the lumen of the gallbladder In the great majority of infected individuals even billions of this organism produce no apparent harm but in a small percentage there is mucosal irritation which is re-

frequently are helpful in providing trophozoites which will confirm presumptive diagnosis, particularly of cecal amebiasis Trophozoites and cysts of *E histolytica* must be distinguished from other intestinal amebas *(E coli, Endolimax nana, Iodamoeba butschlii, Dientamoeba fragilis)*, other intestinal protozoa, *Blastocystis hominis*, tissue cells, and macrophages

Proctoscopy also is a valuable diagnostic technic but its particular usefulness is limited to a study of the sigmoidorectal area and many pitfalls in interpretation occur to confuse the expert as well as those who are unskilled in this technic *Cultivation of amebas* on appropriate media occasionally provides positive diagnosis when other methods have been unsuccessful *Complement fixation* and *intradermal tests* are not routinely satisfactory because of the difficulty in obtaining pure potent antigen

Treatment

As many as 90 per cent of all patients with true amebiasis can be cured Recently acquired amebic colitis, without bacterial invasion of the lesions, is more amenable to treatment than chronic infection Of drugs recommended for this condition emetine hydrochloride the hydroxyquinoline group, and carbarsone are most commonly employed

Emetine Hydrochloride Emetine hydrochloride is the only chemotherapeutic agent which has gained wide recognition for use in extraintestinal amebiasis Its value in amebiasis of the intestine consists almost exclusively in symptomatic relief in cases of acute diarrhea or dysentery, since its cure rate in amebic colitis is relatively low For amebiasis of the liver or other extraintestinal sites the drug is administered by the intramuscular route as a 6 per cent solution Dosage is 1 mg per Kg body weight, but not more than 60 mg per day, for ten to twelve days should be prescribed After thirty days treatment can be repeated

The patient should be instructed to rest in bed and must be watched carefully for signs of myositis and cardiac damage, which may require at least temporary discontinuance of treatment Since extraintestinal amebiasis is secondary to an original focus in the colon, emetine therapy should always be supplemented by oral administration of some other antiamebic drug more satisfactory for eradication of the infection in the intestine

Symptomatic relief in acute amebic colitis is achieved following intramuscular administration of emetine hydrochloride for two to three days, in daily amounts of 1 mg per Kg body weight thereafter its administration is usually not warranted Unnecessary harm has resulted from failure to heed this warning

Chloroquine Phosphate. Recently chloroquine phosphate (aralen diphosphate) has been tested clinically for treatment of extraintestinal amebiasis, and has been found to be a relatively satisfactory substitute for emetine hydrochloride in hepatic amebiasis, although it has not been demonstrated to be curative in amebic colitis A course of treatment consists of an initial dose of 0 6 Gm followed by two to four daily doses of 0 3 Gm Subsequent tests have confirmed the value of chloroquine in the treatment of hepatic amebiasis It is a well tolerated, easily administered drug which can be substituted for emetine

Hydroxyquinolines The satisfactory antiamebic drugs in the halogenated hydroxyquinoline series are chiniofon "diodoquin," and ' vioform "

The author has used *chiniofon* (sodium 7 iodo-8 hydroxyquinoline 5 sulfonic acid) since 1923 and found it to be curative in approximately 90 per cent of all cases of amebic colitis Three or four 0 25 Gm enteric-coated tablets are administered orally three times daily at mealtime for five

terial involvement of the ulcers, sulfonamide and penicillin therapy may be given before, with, or subsequent to antibalantidial medication

Control consists in care not to contaminate food or drink with the excreta of other persons, hogs, or monkeys harboring the parasite

COCCIDIOSIS

This sporozoan infection of man is caused by *Isospora hominis* a parasite of the intestinal epithelium apparently restricted to the lower portion of the ileum It multiplies in the mucosal cells, causing their destruction with resultant pain and exhausting diarrhea

Diagnosis is based on recovery of the typical cyst (oocyst) in the stool No satisfactory chemotherapeutic procedure is known Complete rest in bed and a bland diet for a week to ten days will usually cause the symptoms to abate and the parasites to be evacuated spontaneously, while failure to carry out this discipline may result in chronic infection Control has not been studied

MALARIA

Malaria is infection with protozoan parasites of the genus *Plasmodium* There are four species which produce disease in man *Plasmodium vivax, which causes vivax* malaria (familiarly but inaccurately called 'benign tertian malaria) *P malariae* which causes quartan malaria *P falciparum,* which causes falciparum malaria (frequently referred to as tropical malaria "estivo autumnal malaria malignant malaria etc) and *P ovale,* which causes ovale malaria Vivax infection has an extensive *distribution throughout warm* climates and during the warm season in cooler areas falciparum infection is limited to tropical and subtropical areas quartan infection is essentially a tropical disease and ovale is restricted principally to east Africa The life cycle of these parasites requires an alternation *of hosts* female *Anopheles* mosquitoes in which sexual reproduction takes place and human beings in which the asexual phases and the initiation of sexual development occur Sporozoites, the end products of sexual development in the mosquito are introduced into man when the infected mosquito prepares to take a blood meal The exoerythrocytic prepatent period is an essential phase between the introduction of the sporozoite by the mosquito and the first appearance of parasites in the erythrocytes It is a symptomless period Only when the parasites begin to invade and destroy the red cells in increasing numbers, and the by products of the plasmodia and the parasitized cells circulate through the body does the intoxication syndrome of chills fever, and sweating develop

In the average case of malaria irrespective of the species of *Plasmodium* and *barring complications* an equilibrium is usually established between the host and the parasite following several episodes of this syndrome If this did not occur the host would soon be exsanguinated This control of the parasitemia results from increased activity of the host s phagocytic cells which liquidate the parasites when they escape as naked protoplasts from a *destroyed red cell and before* they invade other red cells Moreover at or before this time, mother sex cells (gametocytes) begin to appear in circulating red blood cells This is the transfer stage of the parasite to the mosquito but it does not have any clinical significance

Diagnosis

Although chills and fever anemia and an enlarged spleen are relatively characteristic of all etiologic types of malaria the potential symptoms are protean depending on the species of *Plasmodium* the virulence of the particular strain *the loca*

sponsible for a mucous diarrhea and pain in the epigastric region Mild gallbladder disease occasionally may be caused by this parasite

Diagnosis of giardiasis is based on recovery of cysts in formed stools, or trophozoites in diarrheic stools and duodenal aspiration *Atabrine* (quinacrine hydrochloride) is satisfactory for eradicating the infection The dosage is usually 0 1 Gm three times daily with meals for five to seven days Chloroquine phosphate 0 1 Gm daily for three to five days is probably equally efficacious Control has not been studied

TRICHOMONAS VAGINITIS

Trichomonas vaginalis is a relatively common flagellate parasite of the vagina and of the bladder and urethra of males It is different from the intestinal *Trichomonas hominis* In men it is usually a harmless commensal but in some women who are infected it produces a distinct type of vaginitis characterized by intense vulval pruritus a profuse vaginal discharge resulting from inflammation and congestion of the vaginal mucosa and at times a dermatitis of the skin areas adjacent to the vaginal os

Diagnosis is made by microscopic demonstration of the motile trophozoite recovered from the vaginal discharge or passed in the urine Treatment consists primarily in changing the *pH* of the vagina from acid to mildly alkaline thus rendering the medium unsatisfactory for the existence of *T vaginalis* This may be accomplished by swabbing the vagina with a green soap solution thoroughly drying the mucous membrane and then insufflating it with powdered sodium perborate Frequently treatment must be repeated a number of times before the infection is eradicated In these instances the sexual partner should be examined as a possible source of reinfection Treatment of the male may involve urethral and bladder installation of mild alkalinizing agents

Neither individual prophylaxis nor group control has been attempted on any appreciable scale

BALANTIDIASIS

Balantidiasis is an infection caused by the ciliate protozoon *Balantidium coli*, a parasite of man hogs, and several species of monkeys It is an occasional parasite of man in the United States and is relatively common in warm climates The organism is the largest of the Protozoa occurring in these hosts, is broadly ovoidal, and is covered with a large number of vibratile cilia The trophozoite lives typically in the wall of the large bowel primarily in the cecal and sigmoidorectal areas Invasion of the tissues is caused primarily by mechanical rather than lytic action of the organism In general the lesions resemble those produced by *E. histolytica* but the neck of the ulcer has a larger diameter and there is less tendency for the organisms to penetrate deeply into the muscular coats Moreover *Balantidium coli* does not produce extraintestinal lesions Symptoms may consist of mild diarrhea or profuse dysentery

Diagnosis is made by the microscopic demonstration of cysts in formed or semiformed stools and of the active trophozoites in unformed stools Care must be taken not to mistake free-living ciliates frequently contaminating stools with the true parasite

Treatment is relatively unsatisfactory but in a few instances carbarsone has been used with apparent success A course of treatment with carbarsone consists of the administration of one to several daily doses of 0 25 to 0 5 Gm with meals followed by monthly stool examinations up to six months to determine the value of the treatment If carbarsone fails to eradicate the balantidia milibis should be employed (0 5 Gm three times daily by mouth for seven days) If there is evidence of bac

pressive usefulness as chloroquine, although it is somewhat slower in resolving the fever

None of the above named drugs is a true prophylactic, that is, they do not inhibit the development of the plasmodium before it establishes itself in an exoerythrocytic focus

Plasmochin, pamaquine naphthoate (N diethylamino isopentyl 8 amino methoxyquinoline naphthoate), has the property of *sterilizing* gametocytes in circulating blood, so that they will not produce infection in mosquitoes When 10 mg of plasmochin are combined with therapeutic doses of quinine or chloroquine, persistent vivax malaria is frequently eradicated However, plasmochin is very toxic and overdoses may result in intravascular hemolysis Hence, the newer, less toxic, yet more effective, antimalarials of this 8 aminoquinoline series have recently been substituted for plasmochin These drugs are pentaquine, isopentaquine and primaquine

With *pentaquine phosphate* (8 [5 isopropylaminoamylamino] 6 methoxyquinoline phosphate) relapses in vivax infections have been practically eliminated by the administration of 30 mg (base) plus 2 Gm quinine sulfate daily for fourteen days Isopentaquine (8 [4 isopropylamino 1 methylbutylamino] 6 methoxyquinoline) when given in the same dosage is regarded as somewhat superior to pentaquine because of the greater margin of safety between therapeutic and toxic dosages *Primaquine* (8 [4 amino 1 methylbutylamino] 6 methoxyquinoline) in the daily dosage of 22 5 mg (base) with 1 Gm quinine sulfate, administered for fourteen days has been found to be even more effective than pentaquine and isopentaquine, with less evidences of toxicity

Control

It is possible to eradicate falciparum malaria in any area and to prevent the transmission of most strains of vivax malaria to the mosquito by regular administration of 'atabrine,' chloroquine, or paludrine to an entire population in a malarious area The present drug of choice for suppressive therapy is chloroquine, which is taken orally as a single weekly dose of 0 3 Gm (=two tablets) on the same day of successive weeks The same objective may be achieved more economically by the use of DDT, or benzene hexachloride ('gammexane') in the destruction of adult and larval *Anopheles* mosquitoes in endemic territory Treatment of clinical cases and gametocyte carriers together with proper application of insecticides constitute a practical control program against malaria

TRYPANOSOMIASIS

Trypanosomiasis is infection with trypanosomes, flagellate protozoa which live in the blood stream and certain tissues of the body Three species produce human disease *Trypanosoma gambiense* (West and Central Africa), *T rhodesiense* (Central East Africa) and *T cruzi* (Western Hemisphere from Northern Argentina to the southwestern United States) The two African trypanosomes are transmitted to man by blood sucking flies of the genus *Glossina*, commonly referred to as 'tsetse flies' *T cruzi* is transmitted by blood sucking bugs of the family *Triatomidae*

In *T gambiense* infection there are three progressive stages following an incubation period of two to twenty three days (1) trypanosomal septicemia (2) lymphadenitis and (3) central nervous system involvement Invasion of the central nervous system produces profound disturbances of the motor and sensory mechanisms with psychic phenomena and the 'sleeping sickness syndrome When there is *T rhodesiense* infection the lymph node involvement develops so rapidly that the patient rarely survives beyond this stage

In *T cruzi* infection the primary lesion (chagoma) may or may not be distinguished Frequently it produces unilateral

tion of lesions in the body, and the age, race, and tolerance of the exposed individual Thus vivax infection may be fatal especially in infants, even though the course of its clinical development is usually relatively benign, while an essentially symptomless carrier of falciparum malaria may suddenly succumb to cerebral complication

Symptoms resulting from re exposure to the homologous strain of the parasite are mild but relatively less immunity is manifest to heterologous strains of the same species and essentially none to other species of *Plasmodium* The development of equilibrium causes the recurrent cycles of chills and fever to be less severe as the infection becomes more chronic and after a time (frequently after about three months in vivax malaria) the cycles disappear For a time the patient is malaria free and parasites are not found in blood films Nevertheless relapse may be expected with a repetition of the original symptomatic period but frequently with less acute manifestations The cause of these relapses is unknown but it is believed that they arise from residual infection in exo erythrocytic foci which become sufficiently activated to spill over into the blood stream

Presumptive diagnosis based on clinical grounds should always be confirmed by microscopic examination of properly prepared blood films

Treatment

For centuries quinine and other cinchona derivatives were depended on as effective therapeutic agents for malaria Quinine is most satisfactorily administered orally as quinine sulfate 1 0 Gm three times a day for two days followed by 0 6 Gm three times a day for five days It is symptomatically efficacious but relapses *frequently occur* Within recent years newer antimalarial drugs have largely supplanted quinine because of their greater efficiency in eradicating the *Plasmodium* Seven of these require special consideration atabrine, chloroquine, "paludrine, plasmochin,' 'pentaquine," "isopentaquine, and 'primaquine" Atabrine, administered orally in doses of 0 2 Gm every six hours for 5 doses, followed by 0 1 Gm three times daily with meals for six days, produces relatively rapid symptomatic relief frees the blood stream of parasites, and in falciparum malaria may produce cure If oral administration is not feasible this drug may be given intramuscularly in daily doses of 0 2 Gm In endemic areas 0 1 Gm per day over an extended period of time suppresses clinical attacks of all types of malaria except a few Southwest Pacific strains of vivax, and prevents parasitemia in falciparum malaria Rarely, temporary mental disturbances result from atabrine administration

Chloroquine Chloroquine phosphate (7 chloro 4 [4 diethylamino 1 methylbutyl amino] quinoline diphosphate), in an initial dose of 0 6 Gm and two subsequent daily doses of 0 3 Gm , produces more rapid symptomatic relief and as high a percentage of cures as the routine clinical treatment with atabrine In endemic areas 0 3 Gm of chloroquine once a week during the period of exposure will suppress clinical manifestations of malaria, except in a few Southwest Pacific strains of vivax, and will prevent parasitemia in falciparum malaria Since chloroquine does not produce yellowish discoloration of the skin or other side effects except occasional pruritus of the palms and soles of the feet, when taken over an extended period of time, it is preferred to atabrine for therapeutic and suppressive treatment, and has largely supplanted atabrine

"Paludrine" Chloroguanide hydrochloride or 'paludrine (1 [p-chlorophenyl] 5 isopropylbiguanide hydrochloride) has practically the same clinical and sup-

by a separate species of *Leishmania* Cutaneous leishmaniasis is caused by *L tropica* and is endemic in northwestern India, the Middle East, Near East, and parts of Africa The mucocutaneous type is caused by *L braziliensis* and is endemic in the forested areas of South America, Central America, and southernmost Mexico Visceral leishmaniasis (commonly called 'kala azar') is caused by *L donovani* and is present in extensive areas of China, India, the Mediterranean countries, Africa, and South America

In cutaneous leishmaniasis there are no systemic manifestations unless the lesions become infected with pyogens In mucocutaneous infection there is considerable systemic reaction and intense local pain at the sites of the secondary lesions In kala azar, following an incubation period averaging about three months, there is a sudden or insidious onset with malaise, fever with one or two daily peaks loss of appetite and weight, edema of the face, chest, and extremities and enlarged tender liver and spleen Frequently, there is associated diarrhea or dysentery bronchopneumonia, and in children a deeply eroding cancrum oris

The demonstration of the leishmania bodies within or breaking out of macrophages in blood films or from scrapings, aspiration, or biopsy of infected tissue, constitutes specific diagnosis

Treatment

In all endemic areas except the Anglo Egyptian Sudan two pentavalent antimony compounds, '*urea stibamine*' and '*neostibosan*' have been found to be satisfactory in treating leishmania infections Urea stibamine (urea salt of *p* carbaminophenyl stibinic acid) is administered *intravenously* as a 5 to 10 per cent solution which is made freshly each time The initial dose is 0 05 Gm, this is increased to 0 2 Gm daily for seven to ten days until a total adult dose of 1 5 Gm is administered The drug is fairly well tolerated but requires careful slow administration to prevent coughing (due to irritation of the respiratory epithelium) nausea, and vomiting Neostibosan (*p* aminophenylstibinate of diethylamine) has come into use more recently and is *probably the drug of choice*, since it has a high cure rate, is better tolerated than urea stibamine, and may be administered either intravenously or intramuscularly The latter route is more practical for children It is available as a 5 per cent solution and is administered as 0 1 Gm on the first day 0 2 Gm on the second day, then 0 3 Gm daily until 2 4–4 0 Gm has been administered

In the Anglo Egyptian Sudan and occasionally in other endemic areas in which patients are refractory to antimony therapy diamidine compounds have been found to be helpful in controlling kala azar The most valuable member of this series is '*stilbamidine*' (4 4' diamidinostilbene) It is administered intravenously as a 5 per cent solution which is made freshly each time The first dose is 0 05 Gm and subsequent doses are 0 1 Gm on the second and succeeding alternate days, until 1 0–1 3 Gm has been administered Patients treated with this drug should be watched with great care for evidence of profound intoxication In some instances facial neuropathy lasting as long as two years has developed as a sequela, on the other hand some clinicians have not observed any ill effects

In cases of cutaneous leishmaniasis in which only a few lesions have developed success has attended *local freezing* with carbon dioxide snow or ethyl chloride *topical radiation* therapy employing 650 r in two equal doses or the intramuscular *introduction of the trivalent* antimonial *fuadin* (sodium antimony III bis catechol 2,4 disulfonate heptahydrate) Fuadin is available as a 6 3 per cent solution and is administered as 0 1 Gm the first day 0 2 Gm the second day, and 0 32 Gm on alter

palpebral edema (Romaña's sign) When the organisms reach the blood stream they may be responsible for an acute typhoidal syndrome frequently observed in young children and lasting about one month If the patient survives this period he usually becomes a chronic invalid, due to lesions produced by the parasites in spleen liver, endocrine organs and particularly the myocardium

Diagnosis

Specific diagnosis depends principally on recovery of the particular trypanosome and its microscopic demonstration In the two African trypanosomiases the characteristic trypanosome is present in circulating blood during the septicemic stage and later during febrile episodes More and more, however dependence must be placed on material obtained from gland puncture and, in *T gambiense* infection, from spinal fluid Specimens must be examined or fixed and stained at once since the organisms degenerate rapidly In *T cruzi* infection the trypanosome is found in the blood only during the early febrile stage and subsequent febrile exacerbations At other times diagnosis is made from gland spleen or bone marrow biopsy by xenodiagnosis (a parasite-free susceptible bug is allowed to feed on the patient and after incubation of the parasite in its midgut to transfer the infection to a small laboratory animal), culture of blood or biopsied material on blood agar medium and specific complement fixation Electrocardiograms and roentgen diagnosis frequently show heart damage associated with *T cruzi* infection

Treatment

For *T gambiense* and *T rhodesiense* infections specific drugs are available for *T cruzi* infection satisfactory chemotherapy is not available Tryparsamide (monosodium N Carbamylmethyl p aminobenzenearsonate) is employed in *T gambiense* infection and is administered intravenously as a 20 per cent solution once or twice a week The initial dose is 1 Gm, with an increase to 2–3 Gm, but not in excess of 35 mg per Kg body weight A total of 21–80 Gm may be required to eradicate the infection If acute optic neuritis develops during the period of treatment the drug must be discontinued immediately to prevent blindness

Suramin (Bayer 205 naphuride), a nonmetallic synthetic preparation is the only satisfactory chemotherapeutic agent for *T rhodesiense* It also is valuable in *T gambiense* infection when tryparsamide is not tolerated It is administered intravenously as a 10 per cent solution for ten weeks in weekly doses of 1 Gm

Some of the *diamidines*, particularly pentamidine have been found to prevent infection for a period of several weeks in laborers who are obliged to spend short periods of time in hyperendemic areas of Gambian trypanosomiasis

Control

[illegible]

sleeping sickness belts clearing out bush and jungle around human habitations, removal of village populations from hyperendemic zones in *T rhodesiense* territory and prophylactic therapy with diamidines The first of these has proved particularly successful The recent use of DDT and gammexane to control tsetse flies may provide considerable help In America trypanosomiasis is combated by the use of these same insecticides as residual sprays to kill triatomid bugs breeding in human habitations while the rebuilding of homes in rural areas to exclude breeding of the bugs has been placed on a practical demonstration basis

LEISHMANIASIS

There are three relatively distinct types of leishmaniasis, each of which is produced

where human excreta are used to fertilize garden crops and sugar beet fields

Diagnosis is based primarily on recovery of the characteristic eggs in the stool If only female worms are present the eggs are infertile and differ in appearance from fertilized eggs In about 5 per cent of infections only males are present and specific *diagnosis must await chemotherapy* A history of atypical pneumonia in an *Ascaris* family or environment suggests the likelihood of a new infection

Treatment

The one satisfactory drug for eradicating *Ascaris of the intestine is crystoids anthelmintic"* (hexylresorcinol pills, 1,3 hydroxy 4 hexylbenzene) Before anthelmintic therapy is undertaken the bowel should be relatively free of food and feces The drug is supplied in a hard gelatin capsule, it is administered on an empty stomach and food is withheld for four or five hours The dose of the drug for adults is two 0 5 Gm tablets, for children of preschool age two 0 2 Gm tablets and for older children three or four 0 2 Gm tablets, depending on the age Two hours after treatment one ounce of sodium sulfate in a glass of water, for purgation, is helpful in expelling the worms and preventing the systemic absorption of their katabolic products Hexylresorcinol should not be chewed or taken with food *Otherwise there are no contraindications It has a worm removal efficiency* of 90 per cent or more It has superseded 'santonin which is much less efficient, and oil of chenopodium which is potentially dangerous in full therapeutic amounts There is no known drug which will kill *Ascaris* larvae during their migration through the lungs

Control entails the education of families so that children are trained to defecate only in a sanitary flush toilet, enclosed outdoor privy, or other type of sanitary latrine All *Ascaris* positive patients must be treated

TRICHOCEPHALIASIS

This infection is produced by the whipworm, *Trichocephalus trichiurus* (or *Trichuris trichiura*) It is prevalent throughout warm moist areas The worm measuring up to 5 cm in length, is delicate, threadlike anteriorly and fleshy posteriorly The females have a bluntly rounded free end and *the males are tightly coiled* The adults live with their head ends sewed into the intestinal mucosa, typically at the level of the cecum and appendix, but in heavy infections they have been found from the terminal ileum all the way to the anus

Diagnosis is based on recovery of the *characteristic eggs in the stool*

Treatment

The only efficient anthelmintic is the crude preparation *leche de higuerón* the milky, viscous sap of the trees *Ficus glabrata* and *F doliaria* which are native to tropical America from Guatemala to Central Brazil The effective principle, ficin is a proteolytic enzyme which digests the exposed part of the worms The crude leche does not damage the tissue of the host but experimental tests by the author (unpublished data) have demonstrated that the refined or semirefined ficin causes irritation and erosion to intestinal mucosa particularly if ulceration is already present The crude drug is efficient only if it has been *freshly obtained or has been* kept at a temperature of about 9° C proprietary preparations in Latin America using 0 5 to 0 1 per cent sodium salicylate as a preservative are only moderately satisfactory *The usual* dose of the crude drug is 60 cc taken by mouth on an empty stomach It has a slightly acrid taste but produces no side effects No purgation is required before or after treatment, as the drug has a mildly cathartic action

Since fresh or refrigerated leche de higuerón is not available, except in a limited area of Latin America substitute treatment which is admittedly less efficient

nate days from the third through the fifteenth day until a total of 40 cc or 2.56 Gm of the compound has been administered

Fuadin has also been moderately successful in treating mucocutaneous leishmaniasis provided therapy is undertaken before mutilating destruction of the lips, nares and nasopharynx has developed as a result of pyogenic complications

In cutaneous and mucocutaneous leishmaniasis bacterial contamination of the lesions may be reduced by the administration of sulfonamides or penicillin Bronchopneumonia and cancrum oris complications in kala azar also respond fairly satisfactorily to penicillin therapy

Control

In India diagnosis and mass therapy with antimony have greatly reduced kala azar in hyperendemic territory, but the disease flared up in the Calcutta area during the famine period of 1945 Studies with DDT sprayed on the walls of homes in Greece Palestine and Italy have indicated the highly lethal properties of this insecticide for the adult sandflies which transmit cutaneous leishmaniasis and kala azar Widespread utilization of such a program would control these two types of leishmaniasis but will not solve the danger of exposure to sandflies infected with mucocutaneous leishmaniasis in sylvatic areas

TOXOPLASMOSIS

Toxoplasmosis is produced by a species of *Toxoplasma*, not distinguishable from *T gondii*, first recovered from a wild rodent of North Africa *Ctenodactylus gundi*, and also recovered from the rat, mouse, *guinea pig, rabbit, dog, birds, and man* The disease for the most part, consists of granulomatous lesions in the brain and chorioretinal tissues, at times it also involves the reticuloendothelium Frequently in infants there are multiple granulomas of the hemispheres, with progressive calcifications Symptoms present at birth or developing in infancy or early childhood consist of convulsions associated hydrocephalus or macrocephalus, and different degrees of unilateral or bilateral chorioretinitis

Treatment

No satisfactory treatment has been developed Sulfonamides arrest but do not kill the organisms Stovarsol' (acetarsone) has some inhibiting effect Streptomycin, aureomycin, and other antibiotics are being investigated

Control of toxoplasmosis will not be possible until the epidemiology of the disease has been fully elucidated Mothers who give birth to a *Toxoplasma* infected infant may have hope that additional children will not be affected

Helminthic Infections (Helminthiasis): A. Due To Round Worms (Nematodiasis)

ASCARIASIS

This infection is produced by the giant intestinal roundworm *Ascaris lumbricoides* It is widely distributed throughout warm climates and relatively common in temperate zones It is particularly prevalent in small children who constitute the principal source of infection for themselves and their elders An exception is found in certain countries such as southern Germany

animal proteins supplemented with oral administration of ferrous gluconate, ferrous *carbonate, or iron ammonium citrate* should be provided for a week or more preceding antihookworm medication Liver extract is not indicated unless there is specific evidence of pernicious anemia

Intestinal Hookworm Infection If hookworm infection is the primary consideration the drug of choice is *tetrachloroethylene* The drug must be fresh and kept in a cool place otherwise it will decompose with a smell of phosgene gas The drug is administered in a single dose on an empty stomach usually in 1 cc or 0 5 cc globules, and should be followed in two hours with 30 Gm of sodium sulfate dissolved in a glass of water to secure purgation Pretreatment with saline purgation is indicated if constipation is present or if fats or alcohol have been consumed during the previous forty-eight hours The adult prescription is 3 cc that for children is 0 06 cc. per Kg body weight up to 15 years With the precautions indicated this drug is essentially nontoxic and has a worm eradication rate up to 90 per cent If hookworm infection is complicated with *ascariasis*, crystoids anthelmintic may be administered or tetrachloroethylene may be combined with oil of chenopodium in the proportion of 9 to 1 (2 7 cc tetrachloroethylene and 0 3 cc oil of chenopodium) with pretreatment and posttreatment purgation with sodium sulfate

'Creeping Eruption' There is no particularly satisfactory therapy for creeping eruption of hookworm origin Killing the migrating larvas at the inner end of the cutaneous tunnels by spraying with ethyl chloride is a commonly employed technic which may be supplemented by topical application of sulfonamides or other antibacterial agents when necessary Hetrazan (1 diethylcarbamyl 4 *methylpiperazine* hydrochloride) administered by mouth is undergoing clinical trial and may possibly be more satisfactory

Control

Diagnosis and treatment of all hookworm infected individuals in an endemic area, together with sanitary disposal of human excreta constitute the demonstrated practical technics of control In association with this program the basic nutritional levels of the population should be raised In "creeping eruption areas dogs and cats should be dewormed several times a year

STRONGYLOIDIASIS

This infection is caused by the threadworm *Strongyloides stercoralis* which occurs in moist warm climates The adult parasitic females are delicate microscopic threads which live in the mucosa of the intestinal tract at any level from the pyloric wall of the stomach to the anus but concentrated primarily in the duodenum and jejunum Here the hookworm like eggs are laid, embryonate, and hatch The larvas escape into the intestinal lumen and are evacuated in the stool On moist soil in a warm shaded environment the larvas feed and are transformed into the filariform stage infective for man As in hookworm infection *Strongyloides* larvas enter the cutaneous venules are carried to the lungs, break out into the alveoli reach the epiglottis and are swallowed Once in the duodenum they begin to burrow into the mucosa, where the females become implanted, and in about twenty-eight days reach the egg laying stage

The adults, their eggs and the hatching larvas which filter through the mucosa to the intestinal lumen produce destruction of the intestinal epithelium and usually appreciable infiltration of eosinophils fibrocytes and epithelioid cells Extensive necrosis at one focus may result in complete denudation of the mucosa Adult female worms are usually prevented from

must be employed The anthelmintic treatment which is recommended is as follows The large intestine is cleansed at night with sodium sulfate sufficient to produce purgation (30 Gm dissolved in a glass of water), this is followed with a high retention enema of tepid isotonic salt solution to remove viscous feces enmeshed among the worms in the cecal area The following morning, on an empty stomach a mixture is taken orally of 2 7 cc tetrachloroethylene and 0 3 cc. oil of chenopodium by adults Children should be given 0 1 cc per year of age up to 15 years Post treatment purgation may be given if required

This treatment will cause evacuation of a majority of the worms in the average infection Two or three treatments usually produce substantial benefit If the worms extend to the sigmoidorectal level, retention enemas of hexylresorcinol (0 1–0 2 per cent in 1 per cent glycerinated aqueous solution) will kill many of them thus permitting removal of the cause of the mucosal irritation and allowing the rectum to recover normal tone Control of the disease consists of the development of sanitary measures especially with reference to disposal of human feces so that exposure is reduced

HOOKWORM INFECTION

Hookworm infection in man is caused by three species *Necator americanus* which is the common hookworm in the warm climates of the Eastern Hemisphere and throughout most of the hookworm belt of the Western Hemisphere *Ancylostoma duodenale* with a distribution primarily in the northern subtropical areas of the Old World and on the west coast of South America and *A braziliense* a less frequent human parasite in warm climates Man is the only important host of the first two species dogs cats and their wild relatives are reservoirs of *A braziliense*

The major damage produced in hookworm infection results from the blood removed by the attached worms and this, in turn, is approximately proportional to the number of worms present in the infection Thus a dozen worms are seldom of clinical interest but several hundred worms characteristically cause a severe blood loss In hookworm belts individuals are constantly subject to reinfection

The *anemia* in hookworm disease is typically a moderate to severe microcytic hypochromic type infrequently in chronic infection it is macrocytic in type As a result of constant blood loss there is dilatation of the heart and tachycardia reduction of blood supply to the periphery loss of weight loss of energy stunting of growth and sexual development mental dullness asthenia, and possibly collapse Hookworm disease is frequently a complication of nutritional imbalance so that at times it is difficult to determine on clinical grounds which etiologic factor is more significant *Ancylostoma braziliense* is not usually an intestinal parasite of man but causes creeping eruption due to the persistent migration of the larvas in serpiginous tunnels through the Malpighian layer of the skin This results in severe pruritus and commonly pyogenic invasion of the lesions due to scratching

In intestinal hookworm infection *diagnosis* is based on recovery of typical hookworm eggs in the stool The number per gram of feces provides a relatively accurate basis for estimating the severity of the infection Creeping eruption of hookworm origin requires differentiation from cutaneous myiasis or 'larva migrans of other types

Treatment

Before undertaking specific therapy the physician should determine the degree of malnutrition and the type and extent of the associated anemia At times two or three transfusions of 500-cc. of whole blood may be necessary to compensate for severe blood loss More frequently, a diet rich in

and are infective for the same or another individual There are four known methods by which infection occurs (1) *direct* anus to mouth inoculation of the same individual by finger transfer, (2) egg contamination of clothing and other objects which in turn contaminate food drink, or fingers (3) air borne eggs which are breathed into the mouth and (4) retrofection, in which eggs hatch on the anal mucosa and the larvas migrate upwards to the cecal region The new infection matures in three weeks or more after exposure and the cycle is repeated The nature of oxyuriasis makes it prevalent in members of a large family or institution where several persons sleep in the same bed or even *in the same bedroom or dormitory*

Enterobius occasionally produces minute ulcers of the cecum or appendix, or may cause hemorrhage from these levels of the bowel, abscesses of the mucosa or submucosa rarely have been credited to the worm More frequently the worms are indirectly responsible for excoriated lesions on the perineal skin, since these result from scratching itching areas In the female the worms may enter the genital orifice and *migrate up into the fimbriated tubules* or even enter the peritoneal cavity *via* this route

Occasionally oxyuriasis is responsible for acute or *subacute appendicitis The worms* crawling out of the anus onto the skin produce a severe pruritus and this in turn because it is scratched leads to an eczematous dermatitis of the area Frequently there are exaggerated nervous reactions in children and young women particularly those who worry about the infection and its stubborn resistance to control Nycturia in boys and nymphomania in girls are at times associated conditions

Eggs are so seldom deposited within the bowel that fecal examination provides evidence of not more than 5 to 10 per cent of the infected individuals Perianal swabbing with Scotch tape on a wooden tongue depressor before defecation or bathing is *the diagnostic technic of choice*

Treatment

Specific therapy should be combined with strict hygienic measures All infected members of a group and frequently suspects or contacts should be given treatment simultaneously The one drug which has been found moderately effective is *methylpararosaniline chloride* in four hour enteric coated tablets to insure the tablet *reaching the cecal level before the drug is* released The dosage is 60 mg three times daily with meals for eight days A week's rest period is allowed followed by a second eight day treatment *For children* under 4 years of age the total daily dosage is 1 5 mg per Kg and for older children 2 5 mg per Kg The interval between treatment days is provided to allow the hatching of any eggs which have remained viable in the environment and have been swallowed during the earlier part of the treatment so that the second period of treatment will forestall a new infection It is for this reason that all worm passers *must be treated simultaneously*

Nausea and vomiting may be anticipated once or twice during the period of treatment but unless there are several severe *episodes therapy should not be stopped.* Experience has demonstrated that reversed peristalsis occurs more frequently with gentian violet therapy in oxyuriasis than in strongyloidiasis Enemas of an *infusion* of quassia chips and other old fashioned remedies are temporarily palliative but are not curative

When gentian violet therapy and *group* hygiene for an entire family proves inadequate, it may be necessary to cleanse the anal region several times daily with soap and water to remove deposited eggs *and* then apply boric acid ointment to the area to relieve irritation from the excess cleans

penetrating through the muscularis mucosae by host cell reaction but in internal autoinfection the larvae pass through without hindrance and thus by internal afferent vessels reach the lungs When larvas and adult worms penetrate bronchial epithelium a severe pneumonitis may develop

The *acute stage*, initiated by maturity of the parasitic females and egg production presents a mucous diarrhea with colicky pains in the pit of the stomach The diarrhea may continue for many weeks and causes severe dehydration and exhaustion Usually, as the infection becomes chronic constipation alternates with diarrhea the latter tending to return following dietary indiscretion During the acute stage a conspicuous eosinophilia (25 per cent or more) is characteristic but not pathognomonic later there is a somewhat reduced eosinophilia and a relative lymphocytosis Lack of eosinophilia in active strongyloidiasis is a poor prognostic sign *Chronic* cases manifest nervous symptoms and at times a state of despondency

Diagnosis is based on the recovery of *Strongyloides* larvas in the stool or by duodenal aspiration

Treatment

Methylpararosaniline chloride (gentian violet medicinal) is the only known drug which is relatively satisfactory for the control of strongyloidiasis This is a combination of pure pentamethyl and hexamethylpararosaniline (i e crystal violet and methyl violet), both of which in sufficient concentration are lethal for the parasitic females The most satisfactory preparation is a one and a half—hour enteric-coated tablet the dose for adults is 60 mg with meals three times daily until 3 Gm have been taken for children under 4 years of age 1 5 mg per kg and for older children 2 5 mg per kg daily for sixteen days One course of treatment will eliminate the ordinary infection, but at times two or three courses are required

Occasionally, patients cannot tolerate continued administration of gentian violet and develop acute epigastric pain, nausea, and vomiting, and sometimes the infection remains refractory to repeated oral therapy Such individuals are cured at times by the transduodenal intubation of 25 cc of a 1 per cent solution of gentian violet crystals (Gentian violet biological should not be used since it contains a varied amount of dextrin which is therapeutically inert) In pulmonary strongyloidiasis and rarely in the intestinal infection a Seitz filtered 0 5 per cent solution of gentian violet crystals in distilled water may be administered *slowly* by vein in an amount not to exceed 20 cc on alternate days, for a total of not more than ten administrations The patient must be hospitalized during this period of treatment, and the heart and kidneys carefully watched for possible damage

No practical program for group *control* has been developed Individuals may prevent infection by protecting their feet with thick soles when walking through contaminated ground

OXYURIASIS (ENTEROBIASIS)

Oxyuriasis commonly referred to as pin worm or seatworm infection, is caused by *Enterobius vermicularis* This infection is cosmopolitan in its distribution but is much more common in cool than in warm climates It is primarily familial in its endemicity The adult worms, measuring 8–13 mm (female) and 3–5 mm (male) in length, are attached to the mucosa of the cecum and appendix When the female becomes gravid it frees itself from the mucosa and migrates down the lumen, crawling out of the anus onto the perianal and perineal skin Here several thousand eggs are deposited in sinuous tracts Within a few hours the eggs become fully embryonated

distribution *O volvulus* occurs in tropical Africa Guatemala southern Mexico and eastern Venezuela *Loa loa* and *A streptocerca* are African in distribution and *M ozzardi* is confined to tropical America

Diagnosis is made on clinical evidence and specifically on demonstration of the particular species of microfilaria for *Onchocerca* from superficial skin biopsy or from visualization of the microfilarias in the eyegrounds and for the other species from blood films However during the biologic incubation period and frequently in chronic filariasis the microfilarias are not demonstrable Intradermal tests with filaria group antigen provide about 90 per cent diagnostic accuracy that the infection is caused by one of the filarias

Treatment

In onchocercosis enucleation of the parent lesion is always indicated In loaiasis the removal of the worm when it crosses in front of the eye or over the bridge of the nose is the procedure of choice In chronic Bancroft s and Malayan filariasis the removal of redundant fibrous tissue is desirable to re-establish lymph flow and for esthetic reasons

Chemotherapy Until recently chemotherapy has not been satisfactory Many trivalent and pentavalent antimonials and arsenicals have been clinically employed with indifferent to fair results Since 1937 Bayer 205 (naphuride) and hetrazan have been given careful clinical trial and appear to be the first effectively lethal drugs for the parent worms Both are well tolerated in therapeutic amounts in Bancroft s filariasis but in onchocercosis the reaction has been moderately severe with the administration of similar dosages

Suramin sodium (Bayer 205 or "naphuride sodium) is given intravenously in the amount of 0 02 Gm per Kg body weight each week for eight weeks (total 0 16 Gm per Kg)

'*Hetrazan* (1 diethylcarbamyl 4 methyl piperazine hydrochloride) is administered orally For Bancroft s filariasis three daily doses of 1 2 mg per Kg body weight (total 0 5–2 0 Gm) over periods varying from three to twenty-one days, have eliminated microfilarias from circulating blood in 13 of 25 filarial patients treated in Puerto Rico in only 1 individual was the drug considered to be ineffective More satisfactory results have been obtained with this drug in the treatment of Bancroft s filariasis in British Guiana and in Africa and *Loa loa* infection in Africa It was relatively well tolerated but in some patients headache nausea lumbar pain adenopathy, rash and other allergic manifestations were exhibited In Mexico and Guatemala *Onchocerca* patients had much lower tolerance for hetrazan Even in daily amounts of 0 5 mg per Kg of body weight patients experienced excruciating pruritus marked edema, temporary visual difficulties chills and fever weakness and prostration However in considerably reduced individual doses a total dosage of 20 mg per Kg body weight (0 1 mg per Kg daily for 20 days) provides a relatively satisfactory anthelmintic regimen for this infection

The reactions to Bayer 205 and hetrazan are probably due to dying microfilarias and parent worms and antihistaminic agents administered concurrently with these drugs relieve the pruritus and other allergic manifestations Since hetrazan is administered orally it is the preferred anthelmintic if it proves effective within the limit of tolerance Several years will be needed to provide a proper evaluation of these potentially useful drugs

Control Since all filaria worms are insect transmitted once the exact breeding places of the insects are known their numbers can be greatly reduced by the

ing Sulfonamide ointment may be helpful in resolving pyogenic infection due to scratching of pruritic skin areas

Oxyuriasis is probably the most perplexing chronic infection which confronts the physician It must be emphasized that meticulous care is required to keep children's fingers clean and to prevent infection from soiled underpants pajamas and bed linens All these should be sterilized daily by boiling if other measures have resulted in failure This infection is uncommon among primitive people in warm climates who wear very few clothes

TRICHINOSIS

Trichinosis is caused by the trichina worm *Trichinella spiralis* It is widely distributed throughout the North Temperate Zone and is infrequently found in the tropics The adult worms of microscopic size inhabit the mucosa of the duodenal and jejunal levels of the small intestine Infection of man results from eating inadequately cooked or processed pork and occasionally bear meat Sixteen to twenty million persons in the United States and Canada have trichinosis

The *pathogenesis* in trichinosis is divided into three successive stages paralleling the life cycle of the worm Severe duodenitis results from the worms invasion of the mucosa Then as the larvas released by the female migrate through the musculature they set up an acute inflammatory reaction They cause irreversible damage in transit through the myocardium Hemorrhage resulting from the migration of larvas through cerebral capillaries may cause severe and at times fatal, nervous and psychic disorders However, 99 per cent of patients are either asyndromic or asymptomatic.

Treatment

There is no specific therapy Symptomatic and supportive treatment are indicated throughout the course of the disease, with alkaline catharsis to keep the bowels open acetylsalicylic acid, and if necessary, opiates to reduce pain and produce sedation, and cardiac stimulants If the infection is suspected within a day or two after its onset sodium sulfate purgation should be administered two or three times a day for several days to prevent the young worms from becoming established in the intestinal mucosa

Control

While meticulous examination of hog muscle samples in slaughter houses and condemnation of infected carcasses will prevent heavy exposure of human beings the technic is laborious and is not carried out in U S Government inspected slaughter houses Thorough freezing of pork will destroy the encysted larvas but frozen pork is less in demand than chilled meat Federal and state regulation to prevent the feeding of raw garbage to hogs is regarded as the most practical method but such control has not met with general acceptance Until one or the other of these measures reduces the degree of exposure it is necessary that all pork be thoroughly cooked

FILARIASIS

The following filaria worms are the common etiologic agents *Wuchereria bancrofti*, *W malayi*, *Onchocerca volvulus* *Loa loa*, *Acanthocheilonema perstans*, *A streptocerca*, and *Mansonella ozzardi* *W bancrofti* causing Bancroft's filariasis and *W malayi*, Malayan filariasis live in lymphatic vessels and lymph nodes *A perstans* and *M ozzardi* reside in body cavities and *A streptocerca* in subcutaneous tissues *O volvulus* is firmly trapped in subcutaneous tumors *Loa loa* migrates through temporary tunnels in the subcutaneous tissue *W bancrofti* and *A perstans* are widely distributed throughout tropical and subtropical areas. *W malayi* is Oriental in

the North Temperate Zone, including northern and central Europe the USSR, Japan Canada and the northern part of Minnesota and Michigan and is known to be established in Chile *H nana* is common in the Mediterranean countries the southern United States and Latin America, it is primarily a parasite of children

Human cysticercosis is rare in the United States but is a serious problem in Mexico and other Latin American countries Hydatid disease is widely distributed throughout Europe the USSR China Australia, New Zealand and South Africa and is a major problem in Lebanon Syria, southern Brazil Argentina Chile and Uruguay Occasional autochthonous cases are seen in the United States Sparganosis is widely distributed including sporadic cases in the United States but its highest prevalence is in French Indo China and Indonesia

Intestinal cestodiasis is acquired by consuming raw or otherwise inadequately sterilized beef containing the larval stage (cysticercus) of *Taenia saginata*, by consuming raw or otherwise inadequately sterilized pork containing the larval stage (cysticerus) of *T solium* by consuming raw fresh water fish containing the larval stage (sparganum) of *Diphyllobothrium latum* by ingesting eggs of *Hymenolepis nana* and by accidentally swallowing fleas or other insects infected with the larval stage of *H diminuta* and *Dipylidium caninum*

Diagnosis

Intestinal cestodiasis varies widely in its clinical manifestations from a symptomless condition to grave intoxication profound anemia and occasionally acute abdomen *Diphyllobothrium latum* is at times associated with and possibly may be immediately responsible for a macrocytic anemia especially in Finland The degree of clinical involvement depends on the species of the worm (and its mass) the age of the patient, and the sensitivity of the patient to absorbed by products of the worm Larval cestodiasis is always of clinical importance but it is particularly a matter of concern when the larvas develop in the central nervous system with symptoms of epilepsy other psychic disturbances or myelitis

Diagnosis of intestinal cestodiasis is based on recovery of the characteristic eggs of each species in the stool (*H nana H diminuta* or *D latum*) or of the characteristic segments of the worm passed in the stool or migrating out of the anus (*T saginata T solium*, or *D caninum*) Presumptive diagnosis of larval cestodiasis can be made on the basis of symptoms to be confirmed by immunologic tests biopsy or at necropsy

Treatment

1 Intestinal cestodiasis Except on rare occasions when surgical intervention is indicated tapeworms in the intestinal tract can usually be eliminated by chemotherapy Of the several drugs available the one most commonly utilized is *oleoresin of aspidium* It is essential that the drug be fresh and administered under a physician's direction In preparation for treatment the patient takes light meals for one or two days and should have saline purgation the night before treatment The drug is administered in the morning on an empty stomach and food is not allowed until copious bowel movements containing the worms have been obtained

The drug may be administered orally or by intubation The former is more frequently employed and consists in giving a total of 4 cc of the drug in three divided doses of 1 3 cc each one half hour apart followed in two hours by 30 Gm of sodium sulfate in a glass of water If proper cooperation of the patient is obtained cures may be expected in approximately 90 per cent of the patients

For intubation the drug is made up in an emulsion consisting of 4 cc oleoresin

application of the insecticides DDT and gammexane," and in this way the transmission of the infections can be eliminated

DRACUNCULOSIS

This infection is usually classed as a type of filariasis but, aside from a superficial resemblance of the adults to filaria worms neither the worms nor the diseases they produce are related

Treatment

Epinephrine is employed for control of the acute allergic episode, which is produced at the time the gravid female migrates from the viscera to the skin Native people remove the worm by gradually winding the free end of the worm on a stick, using great care not to break it off lest the worm die in the long tunnel and a serpiginous abscess develop

Since 1942 effective anthelmintic treatment has been available This consists of the injection of a phenothiazine emulsion into and immediately around the cavity where the worm resides The emulsion is prepared as follows 2 Gm of finely powdered phenothiazine (thiodiphenylamine) is mixed with 0 35 Gm lanolin and 15 cc sterile olive oil previously heated to 150° C for one hour, (2) 5 cc of sterile distilled water is added to make an emulsion, (3) the emulsion is autoclaved in 30 cc bottles at 115° C for thirty minutes The area to be injected should be anesthetized with procaine and a total of 30 cc introduced into the path of the worm and immediately around it The treated area should be massaged briskly for five minutes, and the worm removed with forceps by gentle traction

Control of dracunculosis will be difficult to accomplish because of the custom of infected populations, who bathe in infested water as a religious rite It could be brought about in most endemic foci by raising plankton feeding fish in ponds and shallow wells to eat the infected intermediate host (cyclops) and thus break the life cycle

Helminthic Infections: B. Due to Tapeworms (Cestodiasis)

TAPEWORM infections of man may be divided into two categories those in which the adult worms are present in the intestinal tract and those in which larval stages develop in extraintestinal foci Intestinal cestodiasis is produced by *Taenia saginata* (beef tapeworm), *T solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), *Hymenolepis nana* (dwarf tapeworm) and less frequently *H diminuta* (rat tapeworm), *Dipylidium caninum* (dog tapeworm) and other species Larval tapeworm infections include cysticercosis (produced by the larval stage of *T solium*) hydatid cyst (the hydatid of *Echinococcus granulosus*), sparganosis (caused by infection with the mature larval stage, the sparganum of certain species of *Diphyllobothrium* other than *D latum*), and much less frequently coenurosis (produced by larvas of taenia like tapeworms belonging to the genus *Multiceps*) The mature worm consists of head (the organ of attachment), neck, and a varying number of segments (proglottids) *T saginata* has a normal length of fifteen feet or more, *H nana*, of an inch or less

T saginata is cosmopolitan but is hyperendemic in the Near East and Latin America *T solium* is particularly prevalent in eastern Europe, parts of India, and Latin America *D latum* is typically confined to

and the fluid of the cyst rapidly aspirated with meticulous care taken so that none of the material is spilled into the operative cavity Sediment of the aspirate should be examined microscopically to provide specific evidence (presence of scolices with hooklets) that it is a hydatid The cyst should then be opened, washed with 10 per cent formalin (4 per cent formaldehyde) and the inner wall thoroughly scraped out or, if possible, the entire cyst enucleated The cavity is again treated with 10 per cent formalin to sterilize any remaining scolices, washed out with isotonic salt solution, collapsed, and closed with sutures Then the operative cavity is closed

In hydatid cyst of the lungs clean removal is possible because the cyst is invariably encapsulated In sparganosis, if the invasion is superficial as in the orbital tissues, the worm is removed under procaine anesthesia If the infection consists of multiple or proliferating sparagana widely disseminated throughout the tissues there is no available therapy

Control

The following methods are available for the control of human tapeworm infections (1) sanitary disposal of human excreta (*T saginata, T solium* including cysticercosis *D latum* and *H nana*), (2) thorough cooking of beef, pork, and fresh water fish (*T saginata, T solium*, and *D latum* respectively), (3) periodic deworming of dogs (*D caninum* and hydatid cyst), (4) successful anti rat campaigns (*H diminuta*), (5) boiling or proper filtration of drinking water and (6) avoidance of the application of the flesh of all animals to an ulcerated or inflamed surface or member of the body (sparganosis)

Helminthic Infections: C. Due to Trematodes or Flukes (Trematodiasis)

TREMATODE infections can be divided into four categories (1) those which develop in the human intestine, (2) hepatic flukes, (3) lung flukes, and (4) those which live in portal and caval blood

INTESTINAL FLUKES

These include (1) the large fleshy fluke (*Fasciolopsis buski*), which is contracted from the consumption of certain raw water nuts and bulbs in China, French Indo China, Malaya, Indonesia, and eastern India, (2) the amphistome and echinostome species in which infection results from consumption of a variety of raw vegetable and animal tissues (these species are extensively distributed in the Orient and Africa), and (3) minute forms (heterophyid species) in which infection results from eating raw fish and which is of relatively cosmopolitan distribution

HEPATIC FLUKES

The most common are *Fasciola hepatica* (sheep liver fluke) contracted by man from eating watercress salad in Latin America the Mediterranean countries and Asia *Clonorchis sinensis* (Chinese liver fluke) and *Opisthorchis felineus* (cat liver fluke) which are contracted from eating raw fresh water fish, with distribution in the Orient and in eastern Europe and Siberia respectively

PULMONARY FLUKES

One fluke, *Paragonimus westermani*, is an important parasite of man The infection, referred to as pulmonary distomiasis

of aspidium 30 cc mucilage of acacia and 30 cc of saturated aqueous solution of so dium sulfate This is intubated slowly into the duodenum and the patient must re main in a recumbent position for a half hour before the sound is withdrawn No post treatment purgation is required Intu bation has the advantage of eliminating worms in a considerable percentage of cases refractory to oral therapy Oleoresin of aspidium usually does not kill the worm but narcotizes it so that it is evacuated in an unmutilated state

Carbon tetrachloride by mouth in one dose of 3 cc with pretreatment and post treatment saline purgation is also quite satisfactory however this drug is some what more toxic has more contraindica tions including rapid fatty degeneration of the liver, and digests the head and parts of the worm itself, so that it is difficult to assess the success of treatment from exami nation of the evacuated remnants

Since 1947 *atabrine* (quinacrine hy drochloride) has been given considerable clinical trial for treatment of tapeworm infections and has proved to be as satisfac tory as oleoresin of aspidium in most cases A dose of 0 5 Gm is administered orally on an empty stomach with an equal amount of sodium bicarbonate and is pre ceded and followed by saline purgation (30 Gm sodium sulfate dissolved in a glass of water)

Claims of success for other preparations such as decoction of pumpkin seed and pelletierine, fail if the criterion for cure is recovery of the head Failure to demon strate the head is an admission of unsuc cessful treatment since a new worm will soon develop from a head attached to the intestinal wall At times more than one worm is present in infection with *Taenia saginata T solium* and *Diphyllobothrium latum* while several to many worms are the rule in *Hymenolepis nana* Thus recov ery of a single head does not necessarily provide evidence of the removal of the entire infection In *T solium* infection it is important that nausea and vomiting be prevented since gravid segments regurgi tated into the stomach may disintegrate and discharge eggs which will hatch on re-turn to the duodenum and produce visceral cysticercosis which is much more serious than the intestinal infection If patients harboring this worm provide a history of nausea it may be desirable first to attempt separation of the body of the worm from the head by drastic saline purgation before specific medication is undertaken

2 Larval cestodiasis Extraintestinal in fection by larval tapeworms is not amen able to chemotherapy In cysticercosis of the brain the neurosurgeon usually under takes an exploration of the involved area on the presumptive diagnosis of a space occupying mass Specific diagnosis is then made from the specimen removed Success may be complete or partial if the cysticerus lies in an operable location In hydatid disease the metastasizing uncircumscribed alveolar cyst is inoperable Osseous hydatid is difficult to remove and repair of the damaged bone is a major orthopedic pro-cedure Unilocular hydatid is usually oper able if it has developed in the peritoneal or pleural cavity

Suspicion of this infection may result from a history of a slowly developing tu mor mass in a resident of an endemic area although the patient frequently does not contact the physician until five years or more after exposure If the cyst is hepatic in location it can usually be palpated and thrill may be elicitated on percussion Otherwise it may be suggested by roentgen examination Intradermal reaction to hy datid antigen provides considerable sup-port of a presumptive diagnosis

With the above evidence the surgeon should open the cavity and explore the tumor mass When the cyst is visualized a large caliper trochar should be introduced

cc, fifth day 16 cc seventh day 20 cc ninth eleventh, thirteenth fifteenth seventeenth nineteenth twenty first twenty third twenty fifth twenty seventh and twenty ninth days 24 cc each (a total of 320 cc of the 0 5 per cent solution and 0 6 Gm of *metallic antimony*)

Fuadin (stibophen sodium antimony III bis catechol 2 4 disulfonate) and anthiomaline (antimony lithium thiomalate) are much easier to administer since they are introduced intramuscularly however the relapse rate is high in total doses providing an amount of antimony equivalent to that in the recommended course of tartar emetic therapy If in the treatment of small children it is difficult to enter the veins fuadin should be employed

Control

The variety of ways in which human trematode infections are acquired makes control a difficult problem Consumption of thoroughly cooked vegetable and animal foods would prevent infection with all intestinal hepatic, and lung flukes even in areas where there are animal reservoirs. In Egypt control of *S haematobium* and *S mansoni* is being effected by extensive destruction of the snails which are the intermediate hosts In endemic areas of *S japonicum* infection the problem is more complicated because the snails are difficult to kill and because many mammals serve as reservoir hosts On the whole control of trematode infections of man will require tremendous effort and many years for successful accomplishment

Helminthic Infestations D. Due to Leeches (Hirudiniasis)

LEECHES are annulate worms which are related to common earthworms They have an expansible gut with numerous lateral ceca which become greatly dilated to store the blood which they suck from their victim The medicinal leech (*Hirudo medicinalis*) was familiar to the physician of a century ago and is still employed as a therapeutic agent by Italian Portuguese and some French physicians to reduce blood clots in superficial vessels The most notorious of the strictly aquatic leeches is *Limnatis nilotica* which abounds in pools of fresh water in Egypt Palestine Lebanon and Syria and produces internal hirudiniasis especially of the nasopharynx larynx and trachea Leeches living in a warm humid atmosphere are particularly troublesome to man horses and cattle in tropical rain forest areas of India Burma *Malaya Ceylon New Guinea Borneo* Celebes the Philippines South China Japan and countries bordering on the eastern end of the Mediterranean Sea They cause cutaneous or external hirudiniasis

Treatment

In internal hirudiniasis no specific chemotherapeutic is available but several procedures have been found to be of use In the nares and nasopharynx douches with strong salt water will frequently force the worm to release its attachment it may then be discharged following a paroxysm of sneezing In the throat or larynx the judicious use of procaine will narcotize the worm and allow its removal by gentle traction with forceps However great care must be taken so that the worm does not enter the respiratory tract Occasionally an emergency tracheotomy is required for patients who are suffocating In external hirudiniasis the worm s release may be obtained by applying a pledget of cotton soaked in brine or saturated magnesium sulfate solu

and acquired from eating raw crab meat or crayfishes is endemic in Japan, Korea, Central and South China, Formosa the Philippines, Southwest Pacific islands, and in more limited areas of Venezuela, Colombia, Ecuador, and Peru The related species, *P kellicotti*, a parasite of dogs, cats, hogs, and fur bearing animals in the United States, has been reported in man only once

BLOOD FLUKES

There are three species of blood flukes which commonly parasitize man *Schistosoma japonicum*, which lives primarily in the mesenteric venules draining the small bowel, *S mansoni* in the mesenteric venules draining the large bowel and *S haematobium*, in the vesical and pelvic venous plexuses *Schistosoma japonicum* is endemic in five small foci in Japan, on five of the Philippine Islands, in one small focus in Celebes, and in vast stretches in Central and South China *S mansoni*, in Africa the West Indies Brazil, Dutch Guiana, and Venezuela, *S haematobium*, throughout Africa Syria, Iraq and parts of Iran Infection is acquired from contact with fresh water containing the larvas (fork tailed cercarias) which have escaped from the snail which serves as intermediate host

TREATMENT

For intestinal trematodiasis the drug of choice is 'crystoids anthelmintic' (hexyl resorcinol pills) administered as one dose in hard gelatin capsules on an empty stomach The dose for adults is 1 Gm, for children 0 4–0 8 Gm Two hours later 30 Gm of Glauber salts in a glass of water should be given for purgation

For *Fasciola hepatica* and *Paragonimus westermani* infections *emetine hydrochloride* is relatively specific, and is administered subcutaneously Dosage is determined on the basis of 1 mg per kg body weight (but not in excess of 60 mg) each day, for nine to twelve days If there is evidence of cardiac damage due to administration of the drug, its use must be terminated immediately

For *Clonorchis* and *Opisthorchis* infections the drug of choice is *methylpararosaniline chloride*, administered orally or intravenously This drug is specific and should eradicate the worms in recently acquired infections, however, it cannot reach the worms in the more chronic cases, because of the fibrotic encapsulation around the biliary passages where the worms reside Oral treatment consists of the administration of 60 mg of one and a half-hour enteric coated tablets three times a day with meals for sixteen days Intravenous therapy consists of the slow introduction of 20 cc of a Seitz filtered 0 5 per cent solution of the drug on alternate days for not more than ten administrations Following intravenous therapy the drug will produce a temporary pseudo cyanotic discoloration of the skin caused by the violet color of the solution The drug will then change to its leukobase and the skin discolor will rapidly clear up On contact with the worms in the bile ducts the drug will stain them a violet hue

In schistosomiasis the most effective drug is *tartar emetic* (antimony potassium tartrate) In the vesical type, in which there is essentially no damage to the liver, the adult patient may be able to tolerate a 6 per cent solution In Manson s schistosomiasis a 2 per cent solution is the maximum concentration usually tolerated in schistosomiasis japonica because of the extensive liver damage, a 0 5 per cent solution is indicated The drug must be sterile and introduced into the vein so that none is spilled into the perivascular tissues Also, it must be administered slowly to prevent excessive bronchial irritation, nausea, and vomiting A satisfactory course of treatment with the 0 5 per cent solution providing about 81 per cent assurance of cure, is as follows first day, 8 cc., third day, 12

pulse and rapid shallow respiration These symptoms may subside in a few hours or they may become more severe so that the patient dies of respiratory paralysis

Another group of venenating arthropods consists of *bees, wasps, hornets* and *ants* In the honey bee the stinger is left in the wound, in all other species of bees it is withdrawn as soon as the act of stinging has been completed Some persons are relatively unharmed by these stings with at most a slight local reaction which disappears in a few hours In others the injured member becomes greatly inflamed and edematous and rather profound systemic intoxication occurs Still others on repeated stinging become gravely hypersensitive and succumb unless they are provided with emergency treatment In the tropics stinging ants may cause agonizing pain and at times endanger life

In addition to the arthropods which have thus far been considered as venenating types, certain beetles and the larvas of certain moths require mention Blister beetles (Family Meloidae) cause a vesicating lesion which is accompanied by intense burning pain Several moths have larvas (e g, caterpillars) which are provided with hollow poisonous hairs Common examples of these in the United States are the flannel moth, the puss caterpillar the saddle back caterpillar, the processionary the golden tailed moth the *Io* moth and the range caterpillar When these caterpillars come in contact with the skin or mucous membranes or even when their hairs are blown for some distance into the eyes or nares the hairs are broken off and their hemolytic poisons cause painful local burns

Treatment

If the lesion in arthropod venenation is confined to the site where the toxic substance was introduced and causes only minor pain and itching sometimes it can be relieved by a wet pack of baking soda ($NaHCO_3$) or by application of calamine lotion Intense pruritus is frequently alleviated by rubbing phenolated camphor in mineral oil (3 parts phenol, 6 parts camphor, and 3 parts liquid petrolatum) into the site In honey bee sting the stinger must be removed before the wound will heal In case of shock, cardiac and respiratory stimulants may be needed as emergency measures, epinephrine is usually satisfactory for this purpose Individuals who have a history of hypersensitivity to bee, wasp or ant sting should be desensitized before additional possibly fatal exposure occurs Filtered whole honey bee extract made up in Coca s solution is employed for this purpose and is group specific for all bees hornets and wasps

Ticks firmly attached to the skin should be removed as soon as possible, not only to reduce the amount of trauma and local irritation but more particularly to reduce the danger of tick paralysis and tick transmitted pathogens A pledget of cotton soaked in chloroform should be applied to the attached tick after which it can usually be withdrawn by gentle traction with forceps leaving minimum damage It is essential not to leave the head parts in the skin since this will lead to the development of an abscess or a painful indurated swelling It is equally important not to pull the tick off with one s fingers since this may enhance the chances of infection from pathogenic rickettsias or spirochetes carried by the tick

For *spider and scorpion venenation* palliative treatment sedation and cardiac and respiratory stimulants are usually indicated In addition antivenins are available and should be employed For black widow spider poisoning hyperimmune horse serum (Antivenin *Latrodectus mactans* Mulford s) is a potent standardized therapeutic With evidence that this type of venenation has occurred the patient is first tested for serum sensitivity and if neces

tion The wound may then be staunched by application of a styptic pencil and dressed aseptically to prevent bacterial invasion

Control

Drinking water should be adequately filtered or strained to prevent introduction of leeches into the mouth Persons bathing in water in infested areas must be aware of the danger of leeches entering the nares or urethra Travelers in tropical jungles should wear closely woven pants tucked into leather boots which will not admit leeches Even with these precautions some leech infestation is likely to occur

Arthropod Infestations

ARTHROPODS produce disease in three principal ways (1) by venenation, (2) by invasion of the tissues of the body and (3) by serving as transmitters of pathogenic micro-organisms to man

VENENATING ARTHROPODS

The poisoning properties of arthropods vary widely Bedbugs ticks and certain mites particularly the red mite or chigger (*Trombicula* spp) and the rat mite (*Liponyssus bacoti*) have saliva which contains a toxic principle Certain ticks as the Rocky Mountain wood tick (*Dermacentor andersoni*) may produce an ascending motor paralysis *

Spiders All spiders elaborate venoms which are discharged through their fangs but relatively few species are able to puncture human skin The black widow spider (*Latrodectus mactans*) with a distribution from New England to Chile is a notable example of the dangerous type A red swollen lesion develops at the site of injection with intense local burning and aching As the poison is absorbed into the lymphatics and then is disseminated through the blood vessels dizziness tremors and intense cramps and rigidity of the abdominal muscles may rapidly develop There may be cold perspiration nausea vomiting intense headache moderate elevation of temperature bradycardia and feeble pulse, cyanosis labored shallow breathing difficulty in speech insomnia restlessness stupor, or convulsions and at times shock, delirium, and prostration Death in children is not uncommon

Scorpions Scorpions live in warm climates either dry or moist depending on the species Dangerous species occur in southwestern United States and northern Mexico Central and South America Africa and Asia The more venomous species like the Durango scorpion (*Centruroides suffusus*) of Mexico the black scorpion of Trinidad and the five banded scorpion of the Egyptian Sudan, produce high mortality particularly in children The victim experiences an immediate, intense aching pain at the site of the sting with a burning radiating sensation rapid involvement of the lymphatics draining the region and systemic symptoms including generalized numbness throbbing and twitching of the fingertips toes ear lobes tip of the nose and of the chin, profuse sweating and salivation difficulty in swallowing and speaking vomiting muscle spasm and convulsions strabismus temporary blindness or hemiplegia extreme thirst dysuria or anuria temperature elevation to 104° F or above, quick weak

* See Chapter 8

not affected by the first application Sulfur ointment is prepared as a 5 per cent suspension of the flowers of sulfur in lanolin Pyrethrin ointment is compounded with one volume of 0 75 per cent pyrethrin, 2 volumes of lanolin and 1 volume of vaseline Benzyl benzoate emulsion consists of 25 parts benzyl benzoate 2 parts stearic acid 1/2 part of triethanolamine and 72 1/2 parts of water If the benzyl benzoate emulsion is employed care must be taken to keep it out of the eyes Gammexane ointment (0 5 per cent in an ointment base) has recently been found to be a particularly effective scabicide

Myiasis In myiasis the location of the maggots and the degree of involvement will decide the therapy Intestinal myiasis can usually be terminated by the oral administration on an empty stomach of crystoids anthelmintic Dosage is 1 0 Gm for an adult and 0 4–0 8 Gm for children Two hours later purgation with 30 Gm of sodium sulfate in a glass of water will be helpful in evacuating the worms Urethral myiasis is cured at times by irrigation with a strong solution of sodium chloride or with hexylresorcinol solution 1 2000 in distilled water In case of specific myiasis in which the maggot has tunneled more or less perpendicularly to the surface of the skin procaine or some other local anesthetic should be introduced by needle around the lesion and then into its center so that the maggot is relaxed A linear or cruciform incision is then made to the site of the maggot which is easily removed by tissue forceps If the lesion consists of a tunnel parallel to the surface of the skin the maggot may be visualized at the inner end of the tunnel by massaging a small amount of clear paraffin oil into the skin An incision is made to the worm under local anesthesia and the maggot removed with a sharp needle or forceps When the lesion is in the nasopharynx orbital tissues or in the eyeball a specialist is usually needed to remove the parasite If the lesion is extensive deep and mutilating haste is essential in enucleating the maggots before irreparable tissue damage is done This is followed with irrigation of the wound with a mild antiseptic solution and débridement

ARTHROPODS AS TRANSMITTERS OF PATHOGENS

This section is intended to provide a concise summary of the relationship of arthropods to the transmission of pathogenic micro-organisms and the diseases which they produce Many arthropods are casual mechanical vectors as for example the house fly and other filth flies in the transmission of the etiologic agents of typhoid fever, shigellosis cholera amebiasis and ascariasis fleas blood sucking bugs and mosquitoes in the mechanical carriage of *Pasteurella tularensis* and the biting stable fly *Stomoxys calcitrans* in the transmission of cutaneous leishmaniasis On the other hand there are many species of arthropods which are essential hosts to a large number of pathogens and are therefore true biologic vectors The more important biologic transmitters and the pathogens which they transmit are presented in Table 7

Treatment

The management of arthropod transmitted diseases is primarily a public health problem It consists of one or more of the following types of control (1) reduction in the numbers of arthropod involved to a level below the threshold of transmission (2) interruption of the epidemiologic cycle either before the pathogen enters the arthropod or between the arthropod and man and (3) education of the population as to the ways in which exposure occurs and methods of avoiding exposure The role of the practicing physician is to provide accurate diagnosis of the disease as it

sary, desensitized Then 2 5 cc of the standardized antivenin are injected intramuscularly If symptoms are not relieved in one to two hours a second dose may be administered Scorpion antivenin is not produced in the United States but is available in Mexico, Brazil, Africa, and Asia where there are frequent calls for it In Trinidad one worker has recommended insulin therapy in black scorpion poisoning to protect the pancreas from effects of the hemorrhagic fraction of the venom

Modern insecticides such as DDT, "gammexane chlordane and others now being tested provide a means of control of mosquitoes and many other types of blood sucking flies lice fleas, bedbugs some species of mites and even ticks However, these pests still abound and persons who are particularly sensitive to one or more of these arthropods should take precautions as for example the use of repellents (Rutgers 622) on exposed skin dusting DDT in the socks or in the clothing or avoiding areas or contacts which are infested No control measures have been developed against the black widow spider, scorpions or bees and their relatives Insecticidal spraying of clover and buckwheat fields has destroyed entire hives of bees and thus ruined honey production

TISSUE INVADING ARTHROPODS

Tissue invasion by arthropods may be almost microscopic and confined to the site of contact as for example the introduction of the head of a red mite (chigger) or the stinger of the honey bee into the skin The damage in these cases is usually local and recovery is relatively rapid as soon as the foreign body is removed One species of flea the chigoe (*Tunga penetrans*) burrows deeply into the skin and produces an inflamed swelling the size of a pea It becomes infected with pyogenic bacteria and develops into a painful lesion This infestation is relatively common among the poorer classes in tropical America

Scabies, produced by the mange mite (*Sarcoptes scabiei*) and follicular dermatitis, caused by the follicular mite (*Demodex folliculorum*), are cosmopolitan in their distribution, particularly among the lower classes of the population, and at times tend to become epidemic

Another type of arthropod tissue invader is the fly maggot, which produces *myiasis,* an invasion of the tissues by fly larvas Any surface of the body, as well as the intestinal mucosa and the genitourinary tract may be invaded by these wormlike stages of the fly Moreover, some species have a predilection for depositing their living young or their eggs on essentially uninjured skin or mucous membranes

Treatment

Treatment of lesions produced by arthropods which invade the human body is based on identification of the group of etiologic agents involved and frequently on the circumstances In the red mite (chigger) dermatitis the application of phenolated camphor will relieve the intense itching prevent scratching and guard against sepsis In chigoe infestation the swollen flea must be excised and the lesion cleaned and dressed

Scabies Scabies may be successfully treated with sulfur ointment, pyrethrin ointment, benzyl benzoate emulsion, or 'gammexane ointment The patient s body is thoroughly scrubbed with green soap, soaked in warm water to expose the lesions, dried, and the evident and suspected lesions treated with the scabicide, which is left on overnight The next morning sterilized clothing is put on and all soiled clothing and bed linen are boiled If the infestation is extensive a second treatment (between the sixth and tenth days following the first treatment) will be required to kill larvas hatched from eggs

Poisonous Fishes and Reptiles

FISH POISONING

Man may be poisoned by fishes in one of two ways (1) by eating the flesh or roe of certain fishes, the metabolic products of which contain toxic substances, and (2) by introduction into the skin of poisons of certain fishes through their teeth or spines

Poisoning Due to Eating Fish

A few genera of fishes, notably the puff toads (*Tetraodon* spp), some species of herring (*Clupea venenosa* and *C thrissa*) and porcupine fishes (*Diodonta spp*), elaborate a poisonous principle, which if the fish is eaten raw or cooked, produces serious illness in a few minutes and possibly death within a few hours The poison appears *to have a curare-like action If the fishes* are carefully cleaned, with none of the viscera remaining it is believed that poisoning will not result from their consumption

Treatment Treatment for this type of fish poisoning, just as in instances of acute illness due to eating partly decomposed fish flesh, consists of immediately washing out the patient s stomach, administering saline purgatives, apomorphine, and cardiac stimulants.

Fish Poisoning Due to the Bite or Sting

About thirty species *of eels of the genus Muraena* possess well developed sharp teeth with associated venom sacs The bite of these eels produces a local inflammatory *reaction and at times* a moderate to grave systemic intoxication Many spiny fishes are provided with poison glands situated at the base of specialized hollow spines through which the poison is introduced into the victim s skin The most notorious are the *sting rays,* which have a strong *barbed caudal spine* These sand colored, pancake flat fishes are found in shallow water, *partly covered with* sand, on bathing beaches of the South Atlantic and Gulf Coast of the United States and in many other parts of the world

Other poisonous fishes have the poison apparatus developed in the anterior rays of the dorsal fin *(Scorpaena scropha* and *S plumeri),* in association with the gill cover *(Trachinus draco),* or on the lower jaw (some fresh water catfishes) With entry of the poison barb *into the skin there is a stabbing pain at the site, and rapid development* of an extensive area of inflammation and edema around the wound In addition to the intense throbbing pain of the affected member, there is frequently a generalized reaction which may include *profuse cold perspiration, nausea, vomiting*, diarrhea, dyspnea, tachycardia and rapid thin pulse, delirium, collapse, and rarely death Moreover, extensive hemorrhage into the tissues at the site of injection may result in local gangrene

Treatment Treatment of poisoning caused by fish bite and fish sting *is directed* primarily to rapid management of the primary lesion before systemic absorption occurs The injured member should be tied off with a tourniquet cleaned to prevent pyogenic infection, and if necessary *cut with a cruciform incision to* allow drainage Procaine may be introduced locally to reduce the pain and epinephrine employed to counteract shock

VENOMOUS REPTILES

The poisonous reptiles belong to two groups the lizards, of which the only poisonous species are the Gila monsters (*Heloderma suspectum* of the Western United States and *H horridum* of Mexico and Guatemala) and many species of snakes The Gila ' monsters are provided

appears and to admin ster the most useful therapy Also he must be aware of the epidemiologic s gnif cance of his f ndings and cooperate with public health authori ties so that the disease is brought under control

TABLE 7 ARTHROPODS WHICH ARE IMPORTANT NATURAL B OLOG C VECTORS THE DISEASE AND T E PATHOGENS WH CH T IESE VECTORS TRANSMIT

B olog c ve o	*D a e (and e olog a em)*
CRUSTACEA	
Water fleas (*Cyclop Diap omus*)	Fish tapeworm nfect on (*D phyllobo h um lo um*) Sparganosis (*D phyllobo h um spec es*)
Crabs and crayfishes	Pulmonary dis om a is (*Pa agon mus u man*)
TICKS	
Hard t cks (*Derma en o* et al)	T ck typhus (*Ricke ts a uk* and *R cono*) Q fever (*Coxiella bu n*) Colo ado tick fever (virus)
Soft ticks (*O n thod o* et al)	T k elaps ng feve (*Bo l a du on* et al)
MITES	
Red mites (*Tromb ula spp*)	Scrub typhus (*R ke a orientol*)
Ch cken m e (*Dermany su gall nae*)	St Louis encephali s (us) and Western equ ne enceph alo-myel is (v rus)
Mouse m e (*A lodermany u sangu neu*)	Ricketts alpox (*Rick t a aka*)
LICE	
Body louse (*Ped ulus humanus*)	Ep dem c typhus (*Rick tts a p owazek*) Ep demic elaps ng fever (*Borr l a ecu en*)
BUGS	
Assass n b gs (*T iatoma* spp e al)	Chagas disease (*T panosoma cru*)
FLIES	
Mosqu oes	
(*An phel s* spp)	Mala a (*Plasmod um v vax* et al)
(*Culex* spp *A d s* spp *Anoph* spp and *Manson a* spp)	F la iasis (*W uchere a bancrof* [illegible] *malai*)
(*Aed aegyp* et al)	Yellow fe e (v us) and dengue (us)
(*A d s* spp *Cul x* spp e al)	Equ ne encephalomyel is (irus)
Sandfl es (*Phl be omu* spp)	Leishmaniasis (*Lei hman a donovan L t op ca L b a l ens s*) Sandfly fever (v rus)
Tsetse flies (*Glo na* spp)	[illegible] *T rhod si nse*)
Mango fly (*Ch y ps* spp)	[illegible]
Deer fly (*Chry op* sp)	[illegible]
Black gnat (*S mul um* spp)	[illegible]
FLEAS	
Rat fleas (*Xenop ylla cheop* et al)	[illegible]
Dog cat and human fleas (*Ctenoc phal d can s* et al)	[illegible]

venom throughout the body Transfusion of 300–800 cc of blood plasma should be made if there is evidence of profound shock

Antivenin Administration of antivenin serves to neutralize the venom It may be monovalent, bivalent, or polyvalent, but to be effective it must contain the venom neutralizing substance for the particular snake which has introduced the venom In the neurotoxic type of venenation only prompt administration of the antivenin is effective As soon as possible after the victim has been struck, 20–30 cc of the appropriate antivenin are introduced subcutaneously around the wound to reduce local necrosis Two hours later a similar injection is made along the involved lymphatic tract somewhat more centrally In more advanced cases intramuscular injection is indicated, and in collapsed patients intravenous administration may be advisable It is safer to give an excessive amount of antivenin than too little Patients have been lost because treatment was too conservative Children and infants should have as large an amount as adults, since the amount of venom injected by the snake is approximately the same irrespective of the age of the victim

The antivenin is packaged ready for emergencies in 10 cc. syringes with a needle and is ready for immediate use The site to be injected is first cleansed with alcohol or tincture of iodine, the protecting cap is removed from the needle, air is expelled in the usual manner, the needle is introduced in the site and the appropriate amount of antivenin is injected into the tissues Even though the patient shows rapid improvement, he should be kept under close observation for twenty four hours

Control

Control consists of the wearing of knee length leather boots and closely woven khaki pants tucked securely into the boots Care should be taken not to poke into brush or stones with unprotected hands when passing through snake infested regions In some areas arboreal vipers are common and the head should be protected with a helmet Elsewhere venomous snakes inhabit the rafters of houses as do cobras in India Other cobras in Africa spray their venom several feet, so that eyeglasses are required to protect the eyes Special precautions must be taken with small children to keep them from playing in snake-infested caverns among rocks or on river banks in snake inhabited regions

with two distended poison glands (modified submaxillary glands) one on each side of the lower jaw The bite causes severe local laceration extensive local inflammation, interstitial hemorrhage, intense radiating pain, and in a few hours profuse perspiration, vertigo, tremors and narcosis Since this type of venenation resembles that of pit vipers, consideration of *treatment* for *Gila "monster"* venenation will be included in recommendations for rattle snake poisoning

All snakes elaborate venom but only those groups which have specialized fangs are dangerous to large animals The dangerous types include (1) back fanged species *(Opisthoglypha)* which have the last maxillary tooth modified into a fang of this group only the 'boomslang of South Africa is large enough to attack and venenate man, (2) front fanged species *(Proteroglypha)* which have the first maxillary tooth modified into a fang including the cobras kraits, asps mambas, true coral snakes and sea snakes, and (3) single fanged species *(Solenoglypha)* which have a single maxillary fang represented by the true vipers rattle snakes copperheads water moccasins and their relatives Proteroglyphs inject venom which is primarily neurotoxic, while members of the solenoglyphs (vipers) introduce venom which is principally hemorrhagic in effect

In viperine poisoning there is immediate stabbing, burning pain at the site of the strike, with localized swelling and purplish discoloration of the wound Soon the pain radiates and becomes almost unbearable Nausea, weakness tingling and numbness of the extremities cold perspiration and a feeling of suffocation ensue There may be extensive urticaria and pruritus, extensive hemorrhage of all mucous membranes intense thirst dyspnea, rapid pulse, and prostration Only with the bite of the neotropical rattlesnake and Gabon viper is there a central nervous system syndrome

In the neurotoxic type the early manifestations include prostration and drowsiness, incontinence, salivation, nausea, vomiting and cold perspiration Rapidly spreading muscular paralysis causes difficulty in speech and swallowing, dyspnea, anoxia, and marked cyanosis Respiratory paralysis will produce death

Treatment

This consists of emergency care of the local lesion, supportive treatment, and the administration of antivenin

Local Treatment Local treatment serves to localize, remove, or neutralize the venom before it is absorbed and carried to vital centers In the neurotoxic type of venenation it is frequently necessary to carry out local therapy within two minutes after the snake strikes If the strike is on an extremity a tight ligature or tourniquet should be applied around the member above the wound, although it must be loosened every ten to fifteen minutes to prevent gangrene Immediately following ligation a cruciform incision should be made deep into the wound and suction applied with a breast pump or the lips to drain out the toxic substance Sucking the venom from the wound ordinarily is not dangerous, since digestive juices destroy its toxic properties The application of Epsom salts solution (magnesium sulfate, concentrated solution in water) and ice packs to the wound tend to reduce the edema and inflammation

Supportive Treatment Supportive treatment consists of absolute quiet The patient is placed in a horizontal position, covered with a warm blanket but allowed to breathe as freely as possible Morphine may be administered for sedation and barbiturates to reduce pain and nervousness Strychnine and caffeine are indicated to prevent collapse Under no circumstances should alcohol be given, since it stimulates circulation and hastens distribution of the

which may occur, nor in quoting to him statistics on probable length of life An average for a group of patients cannot be applied specifically to the individual and, even if it could telling the patient, or even his family, that he has so many months or years to live would only produce anxiety and definitely interfere with the treatment. As a matter of fact a doctor who is sufficiently rash to venture a prediction on the probable length of a cardiac patient's life usually finds that he is a poor prophet.

Congestive Heart Failure

ALTHOUGH accidents such as coronary artery thrombosis cerebral embolism subacute bacterial endocarditis an intercurrent infection or other complications may cut short the expected life span, many patients develop congestive heart failure in the later stages of their heart disease Recent intensive investigation has shown that the simple explanation of heart failure as a mechanical damming back of blood into the pulmonary circuit and into the systemic venous system is not adequate The backward failure theory as it has been called cannot explain why heart failure can be relieved by treatment which is not applied to the heart such as with the mercurial diuretics where the action is entirely on the kidney

One ordinarily associates the increase in venous pressure blood volume, and fluid in the extracellular compartment (edema) as primarily related to the failure of the heart itself and possibly as a direct result of decreased cardiac output Yet there is considerable evidence indicating that increased blood volume may result from decreased renal blood flow and reduced glomerular filtration rate and the consequent retention of sodium because tubular reabsorption of sodium is unimpaired It is evident now that the retention of sodium and water in patients in congestive heart failure is largely due to disturbance in the kidney

With the newer physiologic approach to the study of congestive heart failure has come also a re evaluation of the methods used in treatment of heart failure The major procedures include bed rest digitalis and the cardiac glycosides mercurial diuretics and salt restriction

PHYSIOLOGIC BASIS FOR TREATMENT

Bed Rest

Bed rest alone, by decreasing demands upon the heart will often relieve patients of symptoms of congestive heart failure Weight is reduced edema diminished and dyspnea disappears

The use of bed rest is based on sound experimental evidence Dogs with damaged hearts if exercised develop a transient rise in venous pressure If this is done repeatedly chronic heart failure as we know it clinically, results In the patient with heart disease it has been shown repeatedly that heart failure can be produced by physical effort and relieved by rest It is suggested that the effect of bed rest alone should be determined first if possible to gauge accurately the effect of other methods of treatment This does not mean that digitalis and mercurial diuretics should be withheld from the desperately ill patient

Digitalis and the Cardiac Glycosides

Although digitalis has been used in the treatment of congestive heart failure for more than 150 years there is still some

10. *Heart Disease*

ARTHUR C. DeGRAFF

A PATIENT with a disease of the heart does not present a therapeutic problem of only immediate interest but one which will span many years, in fact usually for the duration of that patient's life. Many advances have been made in recent years in the treatment of heart diseases and patients can be made more comfortable and their lives prolonged. In some instances a cure can even be effected, such as in the surgical treatment of patent ductus arteriosus. On the other hand many types of heart diseases are progressive. When a patient with heart disease first consults a physician he often has developed an acute complication associated with the disease, such as coronary artery thrombosis which occurs with arteriosclerotic heart disease or a recurrence of rheumatic fever in rheumatic heart disease, or an episode of acute heart failure. When the acute phase has passed the physician should be certain of an accurate diagnosis of the type of heart disease, the kind and amount of permanent damage, and the extent of cardiac reserve. Each type of heart disease requires special management.

Excellent studies on the natural history of heart disease make possible in many instances a fair appraisal of the stage of disease and a decision on the ultimate prognosis. This is important for the patient's plans for his future and for his family.

The physician should familiarize himself with the patient's habits of living, work, home conditions, and what is perhaps most important of all, mental state. Nearly every patient with heart disease develops a superimposed anxiety state, and unless the patient is well known to the attending physician it becomes extremely difficult to dissociate symptoms due to the heart from those related to anxiety. Many patients are able to work and are usually better if they do work. Patients should be examined at regular intervals even though they may be symptom-free. Such examinations, which need not be more frequent than every three to six months, make it possible for the doctor to chart the course of the disease in any particular patient and permit necessary readjustments in habits of living or prescribe treatment before any serious condition develops.

In the early stages of the management the patient should be given a careful nontechnical explanation of his cardiac condition and the means by which the physician plans to conserve his cardiac reserve. Most patients appreciate being treated as intelligent human beings and resent arbitrary commands and secrecy in methods of treatment. Gaining the patient's confidence helps considerably in management. The doctor must always maintain a feeling of optimism. Nothing is gained by telling the patient about the serious complications

tion in a comfortable, hospital type bed For a change the patient may be permitted to sit in a comfortable chair with the feet resting on another chair or a chair rest Using a bedside commode is usually less strain for a patient than using a bed pan Only in the most extreme state of conges tive heart failure is it necessary for the patient to have assistance in feeding Abso lute immobility on the part of the patient is not necessary nor desirable Anticoagu lant therapy can be given if there is any danger of venous thrombosis *

Bed rest gives a base line for the evalu ation of other forms of therapy Too often medication gets the credit when bed rest has really done the job Thus anyone who attempts to evaluate a new drug in the treatment of congestive heart failure must first determine the effect of bed rest alone, otherwise his data will be meaningless In the early stages of failure other therapy often is not necessary although it is usually desirable to digitalize a patient who plans to return to active work to prevent a re currence of failure A sedative, such as phenobarbital or chloral hydrate, may be needed to make the rest more effective

Digitalis

Although the crude drug powdered digi talis leaf, is still widely used and is when properly standardized a potent and valu able remedy there are now available a number of the pure active principles the glycosides The commonly used *Digitalis*

tains lanatosides A B and C which by hydrolysis give digitoxin gitoxin and digoxin

Not only does the total amount of glyco sides vary from one specimen of digitalis leaf to the next but the percentage of glycoside in each varies For instance, in one lot of digitalis 0 5 Gm of digitoxin was found in 1 Kg, whereas in another 1 Kg lot only 0 5 mg of digitoxin was found This wide variation from lot to lot makes it difficult to be sure of uniformity even though each lot is tested by the U S P standard There is sufficient variation in the rapidity of onset of action and the duration of action of the various glycosides to invalidate the cat bioassay when the drug is used in patients For that reason many manufacturers not only test each new lot of digitalis by the standard U S P tech nic but also undertake clinical trials The doctor who is using the powdered leaf of digitalis should be sure that the prepara tion he is using is an official (U.S P) prepa ration and that it comes from a reliable manufacturer who has had the drug clini cally tested

Eggleston Method of Digitalization. The well known Eggleston method of digi talization is still an excellent one to follow In this technic the total dose required is estimated from the body weight subtract ing for edema The weight of the patient in pounds multiplied by 11 gives a figure for the estimated digitalizing dose in digi talis units Thus, for a 150 pound man the total dose would be 150 × 11 = 16 5 units In most cases each unit is 0 1 Gm al though this is not always so Therefore if the physician prescribes by weight rather than by digitalis units, he should check the particular preparation he is using to make sure of the proper equivalents

If the patient has not had digitalis for at least two weeks half of the estimated dose is given by mouth Six or eight hours later, if the patient does not show signs of toxicity, one quarter of the total dose is given and at the same intervals of time the remaining two doses of one eighth each are given This dosage scheme should be considered as only a rough guide to the dose required Dosage requirements will vary considerably from patient to patient

* See also Chapter 13

question as to how its beneficial action is produced If one of the rapid acting glycosides such as ouabain, is injected intravenously, a fall in venous pressure can be observed in the patient in failure within five to ten minutes Although this effect would appear to be due to an increased efficiency in the heart, it has been suggested that the beneficial effect might be due to a dilatation of the great veins thus causing a drop in venous pressure and relieving the load on the heart However, recent use of cardiac catheterization has demonstrated conclusively that the primary action of digitalis in human heart failure is a cardiac one It is also significant that the venous pressure falls before there is an increase in urinary secretion

Mercurial Diuretics and Sodium Restriction

It has been known for a long time that there is retention of sodium in the body of patients with congestive heart failure Only recently however, the mechanism by which this retention occurs was made clear In congestive heart failure the renal blood flow is reduced sometimes to one-fifth of normal, but at the same time reabsorption of sodium in the distal tubules is normal The amount of sodium reabsorbed does not depend on the percentage of sodium in the tubular fluid but on the absorptive capacity of the tubules themselves This tendency on the part of the body to retain sodium explains why edema occurs as one of the striking clinical manifestations of heart failure There are two methods of attacking this problem One is to restrict the intake of sodium in the diet and the other is to increase the output of sodium in the urine The latter is precisely what the mercurial diuretics do by interfering with the reabsorption of sodium and water by the tubules As diuresis occurs the blood volume is reduced and eventually the venous pressure falls However the action of the mercurial diuretics is entirely different from that of digitalis A digitalis substance will cause the venous pressure to fall in a few minutes after intravenous injection, which indicates the first manifestation of relief from the cycle of congestive heart failure, but the fall in venous pressure after the injection of a mercurial diuretic does not occur for several hours because there first must be an increased urinary output then a reduced blood volume and finally a lowered venous pressure It is interesting to note that patients who have been kept free of congestive heart failure by the use of mercurial diuretics gain in weight and develop edema before a rise in venous pressure occurs when mercurial diuretics are withheld On the other hand patients who have been kept free of congestive heart failure by the use of digitalis show a rise in venous pressure before a gain in weight and the occurrence of edema when digitalis is withheld

There is sufficient evidence to indicate that both digitalis and mercurial diuretics are of considerable benefit in congestive heart failure but the beneficial effects are produced by entirely different mechanisms

DISCUSSION OF THERAPY

Bed Rest

Although bed rest has been one of the earliest forms of therapy in the treatment of heart failure, it has come into disrepute in recent times because of certain complications resulting from complete body inactivity Chief among these complications are venous thrombosis which occurring in the lower extremities may result in pulmonary embolism hypostatic pneumonia muscular atrophy, osteoporosis chronic constipation bed sores and psychic invalidism Most of these complications can be avoided, however by good nursing care which includes care of the skin, massage of the limbs passive exercise and arrangement of the patient in a comfortable posi

TABLE 8 DOSAGE SCHEDULES OF THE COMMONER CARDIAC GLYCOSIDES

Digitalis preparation or cardiac glycoside	*Digitalizing dose*		*Daily maintenance dose (oral)* (mg)
	Intravenous (mg)	Oral (mg)	
Digitalis (U S P)	—	2 5 digitalis unit per Kg body weight in *divided doses*	2 digitalis units
Digitoxin	1 2	8–5 0 average 2 2	0 1–0 2
Gitalin	—	6 5	0 5
Digoxin	0 75 1 0	2 0–5 0 average 3 75	0 5–0 75
Lanatoside C	1 6	7 in 24 hours 16 in 72 hours	0 5 1 0
Ouabain	0 7–1 0	—	—
K strophanthin	0 7–1 0	—	—
Strophoside	1 0	—	—

is given by weight The cat assay units must not be used in giving glycosides and one must never attempt to determine the dose of any glycoside by comparing its cat assay value with that of another glycoside Each *glycoside has its own individual dosage* range which must be learned Table 8 gives *the average oral digitalizing and daily* maintenance doses of the commonly used glycosides

Occasionally as in acute left ventricular failure it is advisable to digitalize rapidly In that case the intravenous route is chosen and one of the rapid acting glycosides such as ouabain lanatoside C or K strophanthin is used After a patient is digitalized it is usually necessary to put him on a maintenance dose of either digitalis powdered leaf or one of the glycosides This dose can usually be given once a day Although the average dose is known for each preparation one must find the proper dose for each patient The correct daily maintenance dose is the smallest amount of digitalis or glycoside which will keep the patient in the optimum condition free from signs and symptoms of heart failure If the patient has auricular fibrillation the ventricular rate may be of some help in gauging the daily maintenance digitalis or glycoside dose Usually the ventricular rate is kept between 70 and 80 per minute at rest However, if the patient has a large heart, his optimum heart rate may be as low as 50 per minute If the patient has regular sinus rhythm the heart rate is affected but little by digitalis

Salt Restriction and Mercurial Diuretics

As stated previously, there are two methods by which the tendency to retain sodium and fluids in the body in congestive heart failure can be combatted One is by rigorously limiting the sodium content in the diet and the other is by the use of mercurial diuretics

Many diets have been devised to lessen the sodium intake * *Eliminating table* salt from the food both at the table and in the preparation of the food will suffice in many instances of moderate *congestive* heart failure particularly if combined with bed rest and digitalis and perhaps an occasional injection of a mercurial diuretic In the later stages however further *restriction is* indicated By the use of salt free bread salt free powdered milk (e g lanolac) *and the choice of foods low in sodium* it is possible to give the patient a fairly low

* See also Chapter 15

The superiority of this method is that the largest dose is given first followed by progressively smaller doses similar to the way a chemist titrates Some patients may not require the entire estimated dose others may need considerably more, in which case one-eighth of the originally estimated dose is given at six to eight hour intervals until the therapeutic effect is obtained or symptoms of mild toxicity occur This method safeguards against exceeding the therapeutic dose which would most certainly occur in many instances if progessively larger and larger doses were used

Cardiac Glycosides The isolation of the active cardiac glycosides from digitalis bodies has made it possible to use pure chemical substances in experimental work It has also brought home the fact that there are considerable differences in the glycosides themselves The latent period (that period from the time of injection to the first measurable effect) varies from a few minutes with ouabain to over one and one half hours with digitoxin The persistence of effect as measured by the rate of dissipation also varies from about twenty four hours for ouabain to almost three weeks for digitoxin The latent period and the persistence of effect of lanatoside C are longer than those of ouabain of digoxin still longer and of gitalin even longer, but not as long as those of digitoxin In general glycosides with a short latent period have a rapid dissipation Because of the extremely long latent period a single dose of digitoxin given intravenously does not reach its full effect for about six hours after injection probably because this glycoside is the only one so far studied that attaches itself for a time to the serum proteins before it is finally transferred to the heart and other body tissues This peculiar feature of digitoxin makes it an undesirable drug to use intravenously whenever a rapid effect of a glycoside is usually desired.

The advantages in the use of the glycosides over digitalis powdered leaf are

1. The drug is of constant potency, so that it can be prescribed by weight Biologic assay is not necessary except as a check by governmental agencies
2. A small tasteless tablet can be prescribed whose potency is considerably greater than that of a similar weight of digitalis
3. A glycoside for any particular purpose can be chosen

It should be emphasized that the pharmacologic action of each glycoside is a digitalis action and if a patient has been given one glycoside or the powdered leaf to the minor toxic point and beneficial results have not been noted it is useless to try another glycoside The toxic manifestations are also the same the only difference being in the duration of toxicity Thus with digitoxin symptoms of toxicity may last for several days whereas with the shorter acting glycosides they are present for only a few hours Nausea and vomiting the occurrence of cardiac arrhythmias such as premature contractions or auricular fibrillation and visible disturbances are the common symptoms of toxicity

The toxic dose for all digitalis preparations is roughly 60 per cent above the therapeutic dose with the possible exception of gitalin for which clinical studies suggest a somewhat greater range

As with digitalis powdered leaf there is considerable variation from patient to patient in the total dose of any glycoside required to produce the full therapeutic digitalizing effect In most instances one cannot digitalize a patient with a single oral dose It would be unwise to attempt to do so because an occasional patient may be rendered severely toxic whereas many patients would not be completely digitalized The principle suggested for digitalis leaf that is giving the largest dose first and then following it by gradually decreasing doses is advocated The dose of each glycoside

One or two tablets should be given once a day after a meal to avoid gastric irritation

The effectiveness of mercurial diuresis may be enhanced by ammonium chloride given up to 3 Gm a day Other agents such as ammonium nitrate potassium chloride urea and sodium dehydrocholate can also be used to enhance mercurial diuresis

The antidiuretic effect of morphine, demerol and possibly other hypnotics or *sedatives must be kept in mind and these* drugs should be discontinued for a time if the expected diuresis does not occur from the injection of a mercurial diuretic

All three commonly used mercurial diuretics are known to produce sensitization reactions such as rash chills and fever, urticaria and a sense of tightness in the chest If such a reaction occurs one of the other mercurials should be used at the next injection because the reaction does not appear to be due to the mercury but to the organic radical of the individual drug Occasionally in edematous persons who have been fully digitalized a rapid mobilization of digitalis from edematous or ascitic fluids may occur with mercurial diuresis and produce acute digitalis toxicity This can be avoided by giving the diuretic in smaller doses and placing the patient initially on a smaller digitalis maintenance dose

Digitalis toxicity occurring after a copious diuresis particularly when manifested by ectopic rhythms may be due in some instances to excessive loss of potassium because the oral administration of potassium citrate (5–10 Gm) has been shown to prevent or eliminate these signs of digitalis toxicity

The rapid removal of edematous fluid is in most instances not necessary or desirable Patients suffer intensely from muscle cramps and weakness in such cases Also it is not desirable to give mercurial diuretics by injection oftener than every third day As a matter of fact serious derangement of the electrolyte balance can occur in too vigorous use of mercurial diuretics, particularly if the patient is on a low sodium diet at the same time Instances of azotemia marked sodium depletion and acidosis have been reported from excessive diuresis *

If fluid continues to accumulate in spite of rest sodium restriction full digitalization and maximum use of mercurial diu*retics, it may be necessary to remove fluid* mechanically from the pleural cavities the abdomen or even from the lower extremities If the blood proteins are reduced the intravenous injection of human serum albumin or blood plasma may be of temporary benefit In patients whose heart failure is accompanied by cyanosis the administration of oxygen by nasal catheter mask or tent is definitely of value

The xanthene diuretics such as theobromine sodium salicylate and theophylline so popular before the days of the mercurial diuretics are rarely used now because they cannot in any way compare with the mercurials in effectiveness

SUMMARY

Patients who are in the early stages of congestive heart failure can often be maintained free from signs and symptoms of failure by reducing their physical activity and placing them on a maintenance dose of a digitalis preparation Excessive salt restriction at this stage is unnecessary During this period many patients are able to work full time without any danger or discomfort There is no need to make them unhappy with too restricted a diet such as rice diet or acid ash diet or by so called dehydration with frequent injections of a mercurial diuretic As the heart disease progresses an occasional injection of a mercurial diuretic may be necessary At this stage many patients will respond satisfactorily on a maintenance dose of digitalis or

*See also Chapter 19

sodium diet, but quite uninteresting and tasteless The diet lowest in sodium content is the Kempner rice diet This monotonous diet consists of rice and fruits It is low in sodium and in protein If it is necessary to place a patient on this diet close medical supervision is essential, and the patient should be in a hospital Salt substitutes usually contain potassium chloride as well as other non sodium containing salts and can as a rule be used freely by the patient They are contraindicated only when there is evidence of renal damage

An ingenious method to allow patients more salt in their diet is the use of cation exchange resins When ingested the resins will exchange ammonium or hydrogen ions for sodium and potassium To avoid potassium loss the resins now available generally replace part of the ammonia or hydrogen by potassium for example (hydrogen cycle 80 per cent, potassium cycle 20 per cent) A negligible amount of calcium is also removed by the cation exchange resins The resins are usually put up in packets of about 10–15 Gm each The average dose is about 40 Gm a day The dose removes about 1 5–3 Gm of sodium or 3–6 Gm of sodium chloride a day If the patient is already on a restricted sodium diet the amount of sodium removed may not exceed 1 Gm per day In the latter case sodium depletion syndrome may occur especially if marked restriction in sodium intake is combined with increased sodium excretion by the use of mercurial diuretics As a rule patients tolerate the resins fairly well Flatulence and constipation are usually the only disturbing symptoms which may occur

The three commonly used mercurial diuretics contain theophylline which protects against local tissue injury at the site of injection It is therefore, possible to give mercuzanthin salyrgan theophylline' or "mercuhydrin intramuscularly as well as intravenously Since on rare occasions death occurs when any of these drugs is injected intravenously, efforts have been made to find a safer drug One which was introduced recently is "thiomerin,' which is similar to "mercuzanthin except that theophylline is replaced by thioglycollate When injected intravenously there does not appear to be any risk of sudden death from ventricular fibrillation and the drug itself causes so little irritation that, except in the most sensitive skins and in edematous areas it can be given subcutaneously Furthermore, thiomerin given subcutaneously, is as effective as the other commonly used diuretics administered by the intravenous route

When a mercurial diuretic is given intravenously, diuresis begins in about one half hour and reaches its peak within four hours The extent of the diuresis depends to a large extent on the amount of edema present although the amount of diuresis varies considerably from patient to patient and even in the same patient from time to time With either the intravenous or the intramuscular route, diuresis can be anticipated in about 90 per cent of patients the chances of success being somewhat greater with the intravenous route Doses larger than 2 cc should not be given, and if dehydration symptoms occur after an injection, it is better to give smaller doses more frequently A word of caution is necessary Patients should not continue to receive frequent injections of a mercurial diuretic if diuresis does not occur because death may result from renal shut down or mercury poisoning

Tablets of "mercuzanthin," 'salyrgan theophylline and 'mercuhydrin" are available for oral use This method of administration is not as effective as the parenteral, but by its use it is possible to make injections of mercurials either unnecessary or less frequent in about 60 per cent of patients The oral route should be tried for at least three weeks before deciding that it is ineffective in any particular instance

Cor Pulmonale

Cor pulmonale either in the acute or chronic form results from an increased resistance to the pulmonary blood flow associated with pulmonary disease In the acute form it is usually seen as a complication of pulmonary infarction in the chronic form it is secondary to emphysema or any other pulmonary disease which can produce pulmonary arterial hypertension Heart failure due to cor pulmonale is characterized by a high cardiac output in the presence of increased venous pressure Pulmonary hypertension associated with mitral stenosis or congenital heart disease is not in this category

Rapid digitalization in these patients is somewhat dangerous because an increase in the already elevated pulmon pressure may occur temporarily if digitalization is done slov period of several days and then are kept on a maintenance dose or a cardiac glycoside most p show some improvement I clinical evidence seems to in digitalis is not as effective in cor as in ordinary chronic congestive ure

The use of oxygen by inhal lieve cyanosis and the admin bronchodilating drugs such as line appear to be fairly effectiv Mercurial diuretics and salt rest aid greatly in removing edema

Arteriosclerotic Heart Disease

ALTHOUGH arteriosclerosis is considered usually as an inevitable accompaniment of general aging it is seen nevertheless in young people It is occasionally present to only a slight extent in old people which emphasizes that other factors than natural aging must play a part Because cholesterol is found in high concentration in the walls of sclerotic blood vessels there is considerable research in progress on the role of cholesterol in the development of arteriosclerosis So far it has been demonstrated that cholesterol in the diet is probably a minor factor if any in the development of arteriosclerosis A popular theory at the moment is that a large molecule of cholesterol may be responsible for the laying down of cholesterol in blood vessels It is suggested that those individuals who have difficulty in metabolizing such large cholesterol molecules might benefit by a low cholesterol diet More important apparently is heredity for it appears that there are families who normally have l cholesterol levels There is evide gest that in these individuals ar sis is more likely to occur Furth may eventually give the answer l there does not appear to be a preventing arteriosclerosis A puzzling is the development of rosis in isolated blood vessels stance, in a branch of a coronary

Arteriosclerosis involving the arteries manifests itself usually ginal syndrome due to coronary sufficiency or the acute ep myocardial infarction which is v though not necessarily associ coronary artery thrombosis

TREATMENT OF CORONAR ARTERY INSUFFICIENCY

In this condition above all ot necessary to adjust the habits of is not sufficient to tell a patient

a cardiac glycoside, moderate salt restriction and one tablet a day of an oral mercurial diuretic Still later, more frequent injections of mercurial diuretics plus ammonium chloride by mouth are needed together with more rigid salt restriction At this time, salt free bread and salt substitutes are used in the diet The cation exchange resins may be introduced into the treatment at this time

Finally, a point is reached where in spite of moderate treatment the patient develops increasing edema The patient should then be hospitalized His treatment prior to admission should be thoroughly reviewed to see whether or not the various items in his treatment have produced the full therapeutic effect He may need more complete bed rest or his maintenance dose of digitalis may be insufficient because there is wide variation in the maintenance dose from patient to patient If one finds that with complete bed rest full digitalis maintenance and the use of mercurial diuretics twice a week the patient is still showing signs of heart failure then rigid salt restriction such as can be obtained with the rice diet should be instituted and the frequency of mercurial diuretic injections increased These procedures should be accompanied by careful studies of blood sodium urea nitrogen creatinine chlorides carbon dioxide combining power and proteins as well as by a study of kidney function The problem at this stage is not simple and the vigorous use of a system or routine may precipitate uremia serious sodium depletion or a disturbance in the acid base balance

At all times in the treatment of congestive heart failure the physician must consider the problem in the individual patient There is no simple routine that he can apply to every case

Two types of congestive heart failure deserve special mention acute left ventricular failure and cor pulmonale

Acute Left Ventricular Failure

Acute left ventricular failure is associated with conditions involving a strain on the left ventricle, such as hypertension or aortic insufficiency and stenosis The attacks frequently occur at night with dramatic suddenness and the clinical picture resembles an acute attack of asthma Most attacks are self limited and short in duration unless the patient becomes panicky The apprehension of the patient can be controlled by the prompt injection of fifteen mg of morphine The difficulty in ventilation and transport of oxygen can be overcome by inhalation of oxygen The acute heart failure is treated by the intravenous injection of 0 5 mg of ouabain followed at intervals of one half hour by 0 1 mg of ouabain until a total dose of 1 0 mg has been administered Before injecting ouabain, one must be certain that digitalis has not been administered within the preceding two weeks An intravenous injection of a mercurial diuretic is not of any value in the acute attack because this drug will not have an effect on the increased venous pressure for several hours

The removal by venesection of 500 cc of blood is beneficial if it is done rapidly and if the patient is not anemic Just as effective however and less dangerous is the so called bloodless phlebotomy Blood pressure cuffs are applied to all four extremities and the pressure raised in the cuffs sufficiently to obstruct venous return but not arterial flow A considerable portion of the circulating blood can be trapped temporarily in the extremities by this technique Care must be taken in releasing the cuffs so that there is not a sudden overloading of the circulation To prevent the recurrence of an episode of acute left ventricular failure the patient should be kept on a maintenance dose of digitalis he should avoid heavy physical work, get plenty of rest, and avoid becoming overweight

If the patient is asymptomatic at the end of two weeks and otherwise appears to be doing well nursing care can gradually be dispensed with, although it is usually desirable to keep a nurse in attendance during the day for at least another two weeks During the fourth week, the patient can usually be permitted to read, listen to the radio and even have a television set in his room Visitors who do not excite the patient or stay longer than a few minutes are also permitted in the fourth week Later the patient may be allowed out of bed to sit in a chair and go to the bathroom Activities thereafter can gradually be increased

After the first few days the diet can be made more liberal by the gradual addition of solid foods The meals should remain small and rich, highly spiced foods and iced drinks should be avoided A mild cathartic, such as milk of magnesia is occasionally needed, but it is not necessary for the patient to have an evacuation every day

Sedatives should be stopped as soon as possible This is done usually by gradually cutting down the dose and frequency Oxygen therapy is rarely needed after the first few days but it is probably a good plan to keep an oxygen cylinder on hand for another week or two in case of emergency Since papaverin and aminophylline although commonly used as part of the treatment of coronary artery thrombosis are drugs of doubtful value they most certainly are not needed after the acute phase of illness is past Dicumarol should be continued for at least five weeks and then the dosage should be gradually reduced over the next ten days before stopping altogether There are some patients particularly those prone to repeated episodes of coronary artery thrombosis who should be maintained indefinitely on a dose of dicumarol adequate to cause the prothrombin time to remain between 25 and 35 seconds *

After the patient has reached the point where he is able to go outdoors the amount of walking that he does each day can be gradually increased He should be warned not to exert himself to the point of fatigue or chest pain As a general rule it is not desirable for a patient to go back to work in less than three months and the majority need a six months period for rehabilitation Most patients are eventually able to return to work Problems of rehabilitation in some patients are more difficult to solve than the immediate treatment of the acute attack Change of job and even change of residence may be necessary, particularly for those whose previous employment involved considerable physical or mental strain or long hours of traveling to and from work If the cardiac reserve is so limited that gainful employment is contraindicated careful preparations must be made to occupy the patient's time by his absorption in a hobby Among hobbies suitable for the totally disabled heart patient are painting photography music, stamp collecting and writing In many parts of the country there are now available specially trained vocational counsellors who can determine what hobby should be followed The scope of the patient's activities must be considered not only from the point of view of his medical condition but also from that of his education, mentality, and social interest There should be ample opportunity for even the totally disabled patient to get considerable enjoyment out of life and thus avoid the anxiety neurosis which is certain to appear in the person with nothing to do

* See Chapter 13

slow down in his work and avoid sudden severe physical effort

Readjustment should include a reduction in weight if the patient is overweight change in job if that seems indicated change of environment depending on conditions in his home and other social factors and above all else elimination of anxiety even if it is necessary to refer him to a psychiatrist although this is not usually necessary if the physician will take enough time with the patient The anxiety factor must be controlled otherwise the patient unnecessarily may consign himself to a life of total invalidism

In general patients who do not smoke get along better than those who continue to smoke Smoking certainly should be discouraged in those who develop chest pain an increase in heart rate or premature beats after smoking Since there is some evidence that an increase in carbon monoxide in the blood occurs in smokers which lessens available oxygen for the heart it would seem reasonable to advise patients with coronary artery disease against the use of tobacco In most patients coffee should also be eliminated because of its effect on the central nervous system It increases nervous tension and also causes an increase in heart rate Alcohol in moderation on the other hand is helpful in that it produces general relaxation and may possibly produce some coronary artery vasodilatation

Sedatives are usually of some help at the beginning but care must be taken that the patient does not become dependent on the sedative Phenobarbital 0 03 Gm two or three times a day is probably the best This drug should be stopped as soon as the patient has made the proper readjustments in his living habits

Nitroglycerin

Nitroglycerin is probably the best drug for its effect on the coronary arteries Unfortunately its action is brief There is not however, any contraindication to the use of this drug at frequent intervals The exact dose for each patient is important because headaches and dizziness develop if the dose is too large and no therapeutic result occurs if the dose is too small The average dose is 0 4 mg It acts as a powerful vasodilator to the coronary arteries It must be remembered however, that spasm other than in the coronary arteries is also relieved by nitroglycerin so that one is not justified in concluding that because relief of pain occurs after the use of nitroglycerin the pain is of cardiac origin

Other Drugs

Other drugs in the nitrite group are not as desirable or as effective as nitroglycerin *Amyl nitrite* by inhalation is rather violent in its action and the pungent odor usually embarrasses the patient if he find it necessary to use the drug when other people are about *Erythrol tetranitrate* and *mannitol hexanitrate* are long acting and would be more useful if the incidence of side reactions such as headache and dizziness were not so common Other so called coronary vasodilators are of questionable value

Experimental work on animals indicates that members of the xanthene group particularly *aminophylline*, can produce considerable coronary artery dilatation Clinical studies have been equivocal Several studies using placebos for controls have not revealed any difference between aminophylline and the placebo On the other hand when the tolerance to breathing 10 per cent oxygen was studied it was found that giving aminophylline either intravenously or by mouth produced a greater tolerance for diminished oxygen inhalation The general clinical impression from the use of aminophylline appears to be that its effect if any is only moderate when given by mouth

Papaverin has also been shown to have some coronary artery dilating effect in ani

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* See Chapter 13

*Hypertensive Heart Disease**

A PATIENT is not considered to have hypertensive heart disease unless some cardiac abnormality, such as cardiac enlargement, abnormal electrocardiogram or symptoms of heart failure, is associated with the elevated blood pressure. The height of the blood pressure does not bear a close correlation to the cardiac involvement. As a matter of fact, patients are known to have blood pressure levels of over 200 mm. Hg systolic and 140 mm. Hg diastolic for years without any evidence of cardiac involvement, while others show serious cardiac embarrassment with blood pressure levels only slightly above the arbitrary upper limit of normal. The frequent association of coronary artery sclerosis with hypertension also complicates the problem.

The treatment of the hypertensive patient requires a thorough knowledge of the patient's personality, his problems and his background as well as the usual medical facts obtained by examination. Careful psychiatric studies on hypertensive persons have indicated that an emotional pattern of repressed hostility is common to this group. Although an occasional patient has had considerable improvement from psychotherapy, in general the results from this type of therapy alone have been rather disappointing.

In nearly all types of treatment suggested for patients with hypertension, there is the assumption that a reduction in blood pressure is not only desirable, but that if the blood pressure can be brought down to and kept within the average normal range, the patient will be considerably improved. Since the elevation of blood pressure can be due to many diverse physiologic functions, it follows that its mere reduction does not mean that the cause of the disturbed physiologic mechanism has been successfully attacked. It has been pointed out already that elevation of the blood pressure per se is not inconsistent with good health and even long life, and that the height of the blood pressure cannot be correlated either with cardiac involvement or life expectancy. Considerable research is necessary before an entirely rational and satisfactory therapeutic approach to the treatment of hypertension can be determined.

* See also Chapter 15.

Rheumatic Heart Disease

RHEUMATIC heart disease presents its own peculiar problem in treatment because there is a tendency for episodes of acute rheumatic fever to recur. Although a recurrence is possible at any time, the greatest danger exists in the three years immediately after an attack. Since the introduction of the sulfonamides, considerable attention has been directed to prophylaxis by preventing Group A β hemolytic streptococcus infections of the throat which precede the active rheumatic state. It is well established that sulfonamides, such as sulfadiazine 1–2 Gm. a day by mouth, will prevent Group A streptococcus throat infections with the exception of types 17 and 19, which are sulfonamide resistant strains. Since none of the types of Group A streptococci associated with rheumatic fever appears to have developed resistance to peni

cillin it was natural that oral preparations of this drug should be tried as a prophylactic agent At present it is known that one penicillin tablet of 100 000 units given at least one half hour before breakfast and another tablet given three hours after the evening meal is quite effective against β hemolytic streptococci in the throat but not against α strains Because only the β hemolytic strains of streptococci are associated with rheumatic fever it would appear that oral penicillin is a fairly effective method of preventing a recurrence of rheumatic fever The high cost of the penicillin tablets is still a deterrent to its general use Recent studies with dibenzyl penicillin (a long acting penicillin) suggest that a single injection of 1 200 000 units may give low but adequate blood levels up to one month Thus it may be possible with this new preparation of penicillin to protect against infection with Group β hemolytic streptococcus—and thus against rheumatic fever—by injections once a month Measures to prevent the spread of air borne infection such as ultraviolet radiation glycol vapors and oiling of the floors and blankets in dormitories undoubtedly lessen the spread of streptococcus infections and thus rheumatic fever The use of penicillin aerosol and powder preparations by many people for throat infections may also have contributed to the reduction in rheumatic infection in the past few years

TREATMENT OF ACUTE ATTACK

The treatment of the acute attack of rheumatic fever has been made much easier with the advent of cortisone and ACTH Although both these drugs will cause a rapid and remarkable disappearance of the acute manifestations of rheumatic fever, there is still considerable doubt as to what effect if any they may have on the prevention of permanent cardiac damage For that reason a cooperative study is under way in many hospitals throughout this country to determine the comparative value of cortisone or ACTH and salicylates in the treatment of rheumatic fever A preliminary report of the study indicates that in general salicylates in adequate dosage are about as effective as ACTH or cortisone Many patients particularly those with mild symptoms get along quite well on salicylates alone The dosage used will depend on the individual patient but it is rarely necessary to exceed 6 Gm of sodium salicylate given in divided doses throughout the day Amounts exceeding 10 Gm per day may cause severe toxicity and even death Studies on salicylate blood levels in patients receiving the drug indicate wide individual variation in absorption of salicylate from the intestinal tract

For cortisone the cooperative study group recommends that 300 mg be given the first day 200 mg the second then 100 mg a day for the next three weeks after that the dose should be reduced gradually The total dose for the entire course is 4 5 Gm Four doses of procaine penicillin (300 000 units each) may be given initially by injection every other day to eliminate streptococci from the throat or circulating blood Because cortisone tends to cause fluid retention and potassium loss patients are limited as to sodium chloride in the diet and are also given 1 Gm of potassium chloride orally Toxic reactions to cortisone are not usually severe Occasionally acne is a troublesome complication The moon face noted during treatment disappears quite promptly soon after treatment is discontinued Personality changes particularly depression may occur but they also disappear if treatment is discontinued

Patients with rheumatic activity should remain in bed until all signs of active infection have disappeared The diet should be well balanced and sufficient in amount so that the patient does not lose weight Because anemia frequently develops tablets

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to penicillin then a dose of 2 400 000 units a day should be given divided into eight intramuscular doses of 300 000 units each every three hours day and night This is continued for two weeks at the end of which time if the temperature is normal and all other signs of infection have subsided a single daily injection of 600 000 units of procaine penicillin is given for the next four weeks Larger doses are indicated if the organism recovered from the blood stream is not particularly sensitive to penicillin or if a positive blood culture could not be obtained Doses up to 20 000 000 units a day have been used in some cases When such large doses are given potassium penicillin should be used When penicillin is not effective streptomycin may be of value However if the streptomycin dosage exceeds 2 Gm a day for more than a few days permanent vestibular damage may result The usual dose is 1 Gm a day Good results are sometimes obtained by the combined use of penicillin and streptomycin

Aureomycin terramycin or chloramphenicol may be used if the organism obtained from the blood stream is sensitive to any of these drugs and resistant to penicillin or streptomycin

Although a patient may recover from the infection he still has a damaged heart Occasionally the damage has been so great that the patient dies even though at autopsy healed ulcerative endocarditis is noted It is therefore, important to start treatment as early as possible and to use adequate amounts of an antibiotic for a long period of time

Congenital Heart Disease

WITHIN recent years several types of congenital heart disease have been treated surgically with considerable success Patent ductus arteriosus and coarctation of the aorta can be completely corrected by surgical measures providing that the operation is done early in life

Marked improvement may occur from the surgical treatment of pulmonic stenosis Recently an ingenious operation for interventricular septal defect has been reported

Cyanotic children who have the tetralogy of Fallot (patent interventricular septal defect pulmonary stenosis dextroposition of the aorta and enlargement of the right ventricle) or one of the related conditions can be benefited in some cases by an anastomosis of one of the subclavian arteries to the pulmonary artery This allows at least a portion of the poorly oxygenated blood to be sent through the pulmonary circulation where oxygenation can occur It is remarkable how well many of these children look after an operation of this type It is too early to know what the ultimate prognosis will be but follow up studies indicate that patients operated on several years ago still are doing well

Before considering a patient with congenital heart disease for operation a thorough cardiovascular study should be made This includes of course the usual fluoroscopic examination and electrocardiogram In addition the following procedures may be necessary in some cases for accurate diagnosis (1) angiocardiography with diodrast or neo iopax (2) cardiac catheterization studies to determine right auricular right ventricular and possibly pulmonic artery pressures samples of blood being taken from these areas so that oxygen saturation can be determined and the cardiac output calculated and (3) particu

of ferrous sulfate, 0.2 Gm. two or three times a day, may be necessary. Unfortunately, if the infection is severe, the oral administration of iron may not be of much value and transfusion of whole blood is then necessary. It is usually advisable to give supplementary vitamins: one or two multivitamin (U.S.P.) tablets a day plus one 50 mg. tablet of ascorbic acid are usually sufficient. If heart failure develops the treatment is the same as that for heart failure from other causes. It must be remembered, however, that in some patients rheumatic activity may be so severe that heart failure may get worse in spite of vigorous treatment. In such instances the prognosis is exceedingly grave.

MANAGEMENT

Many patients who have had rheumatic fever present no clinical evidence of permanent cardiac damage. The major problem for these patients is the prevention of a subsequent attack of rheumatic fever. Prophylaxis with either sulfadiazene or oral penicillin is advisable for at least three years after an attack. These patients can lead a normal life with no restriction in physical activity required. However, it is desirable to avoid as much as possible situations which might lead to upper respiratory infections with streptococci.

Even those patients with permanent valvular heart disease get along well for many years. They should, of course, be under careful medical supervision. If heart failure develops, proper treatment should be instituted immediately. Patients with mitral stenosis may develop auricular fibrillation and then may require digitalis maintenance if regular rhythm cannot be restored by the use of quinidine. A distressing complication in these patients is the occurrence of embolic phenomena due to thrombus formation in the left auricle. Some of these patients will require dicumarol medication on a daily maintenance basis.*

Surgical treatment for the relief of mitral stenosis now offers some hope for patients who would be otherwise chronic invalids. Mitral commissurotomy is now a well established surgical procedure, and in properly selected cases can make considerable improvement in cardiac hemodynamics. The surgical risk is gradually being lessened by improvements in technic, so that even far advanced cases of mitral stenosis are now being operated on with considerable success.

* See Chapter 13.

Subacute Bacterial Endocarditis

THIS disease, which in the pre-antibiotic days was uniformly fatal, can now be arrested in about 80 to 90 per cent of instances. The number of "cures" has risen as the dosage of penicillin has increased. In the early days of the use of penicillin it soon became evident that amounts of penicillin sufficient to treat pneumonia were wholly inadequate for subacute bacterial endocarditis. Dosage advised now depends a great deal on the sensitivity to penicillin or other antibiotics of the bacteria obtained from the blood stream. It is, therefore, important to make a determined effort to obtain a positive blood culture before starting treatment. Blood cultures should be taken daily for five days and then treatment with penicillin should be started, because to wait longer would permit further destruction of the heart valves. If a positive blood culture has been obtained and the bacteria are quite sensitive

Cardiac Irregularities

BEFORE attempting to treat a cardiac irregularity, it is important to know exactly what type of irregularity is present because the treatment depends on an accurate diagnosis Some irregularities such as premature contractions, are of minor importance and frequently are not associated with organic heart disease others such as ventricular tachycardia are serious and require immediate treatment The diagnosis can readily be made by means of the electrocardiogram but in many instances it is possible to make an accurate diagnosis without it

PREMATURE CONTRACTIONS

Premature contractions are commonly described by the patient as 'skipped beats" or as "a feeling as though the heart were turning over ' Premature contractions may be of auricular auriculoventricular nodal, or ventricular origin Ventricular premature beats are about six times as common as the other two types combined Premature contractions are often noted in individuals who use tobacco, coffee, or alcohol to excess In such instances, merely stopping the toxic agent which has apparently caused the increased cardiac irritability often is all that is necessary

If the premature beats tend to persist in spite of correction in habits of living then quinidine can be given in doses of 0 2 Gm three times a day for two or more weeks The dose of quinidine can be increased or decreased depending on the needs of the individual patient but it is rarely necessary to give more than a total of 2 Gm of quinidine a day Patients who are sensitive to quinidine can receive digitalis which has also been shown to depress cardiac irritability when given in therapeutic doses Digitalis is not suggested as the drug of choice because digitalis itself can produce premature contractions when given in toxic doses Pronestyl (procaine amide) orally to the amount of 0 5 Gm three or four times a day may be given to patients who have an idiosyncrasy to quinidine The combined use of ' pronestyl and quinidine may be tried when either drug alone cannot be given in large enough quantity because of side effects Ventricular premature contractions also occur in recent myocardial infarction Quinidine is the drug of choice for treatment then Auricular and auriculoventricular premature contractions are frequently seen in acute rheumatic fever In that case, no specific treatment for the premature contractions is necessary

PAROXYSMAL TACHYCARDIA OF SUPRAVENTRICULAR ORIGIN

Supraventricular tachycardia, that is, auricular or auriculoventricular nodal tachycardia, occurs in paroxysms characterized by the sudden onset of rapid regular rhythm with a heart rate usually exceeding 180 per minute and the equally sudden return to normal rate after a period of time which might be a few seconds in some attacks or several days in others These attacks usually occur in persons who do not show evidence of heart disease between attacks Attacks of short duration do not require treatment However if an attack persists for several hours the patient may become quite uncomfortable and efforts should be made to terminate the attack Simple measures such as carotid sinus pressure eyeball pressure holding the breath and performing the Valsalva experiment (attempting to expire against a closed glottis), should be tried first Strong vagus stimulation produced by emetic drugs such as syrup of ipecac given by mouth may end the attack However, such a pro-

larly in the cyanotic patients, determination of the arterial oxygen saturation The data obtained must then be carefully analyzed and discussed with the surgeon to decide if an operation should be attempted In some medical centers, a team of specialists and technicians is responsible for the special technics thus assuring a smoothly functioning unit which can furnish accurate data

Syphilitic Heart Disease*

WITH intensive efforts all over this country to treat syphilis in its early stages syphilitic heart disease is becoming rare However it is seen sufficiently often for the physician to remain alert for it Early diagnosis is important because treatment instituted then may slow down the course of the disease and may even arrest it The presence of aortic insufficiency or localized dilatation of a portion of the aorta particularly the first portion, should lead the physician to make the necessary serologic tests for syphilis The treatment for syphilis is use of penicillin There is a difference of opinion concerning the amount of penicillin to be given in one dose and the length of time for it to be continued It would seem if any error is made it is best to make it on the side of too much rather than too little Three hundred thousand to 500 000 units of penicillin given intramuscularly each day for a period of two weeks is probably sufficient although it is too early to tell whether all cases are adequately treated by this dose No bad effects are noted on the cardiac condition by the resolution of the active syphilitic process Bismuth can be given in addition either by injection or by mouth

If the patient with syphilitic heart disease goes into congestive heart failure, the treatment of his heart failure is the same as with heart disease of any other etiology If an aneurysm is present and appears to be increasing in size, the possibility of introducing a wire into the aneurysmal sac to aid formation of a clot should be considered

* See also Chapter 59

Thyrotoxic Heart Disease*

WHEN cardiac disorders are due to overactivity of the thyroid gland the removal of a sufficient portion of the gland surgically will usually cause all cardiac manifestations to disappear The problems in treatment of the cardiac disorders themselves are similar to those in other types of heart diseases with the exception that the response to therapy is usually not as prompt or complete because of the increased basal metabolism For instance, larger doses of digitalis are usually required for maintenance in the treatment of congestive heart failure It is often difficult in the presence of auricular fibrillation to keep the ventricular rate below 100 per minute even with large doses of digitalis Where surgical treatment is contraindicated satisfactory results can often be obtained by adequate daily doses of propylthiouracil, or by the use of proper doses of radioactive iodine

* See also Chapter 29.

to stop the rhythm of auricular fibrillation by the use of quinidine should be made because such treatment is effective in at least 50 per cent of instances If the patient is not sensitive to quinidine, 0 4 Gm can be given every three hours until normal sinus rhythm is restored a total dose of 2 Gm is reached, or the patient shows signs of quinidine toxicity The attacks may be prevented by the prophylactic use of quinidine or 'pronestyl

AURICULAR FLUTTER

This rhythm considered generally to be due to a circus movement in the auricles is related to auricular fibrillation but the circus rate is much slower usually under 300 per minute The ventricular response is usually 2 1 or 3 1 Auricular flutter should be suspected in any patient who has a regular rhythm of about 120 per minute without any apparent reason Quinidine usually does nothing more than slow the flutter rate, the circus rhythm is rarely broken The best procedure is usually to change auricular flutter to auricular fibrillation by a full therapeutic dose of digitalis and then to stop all medication to see whether or not sinus rhythm will restore itself spontaneously This usually occurs If auricular fibrillation persists quinidine can then be given with much greater hope of success than if the drug were used when the rhythm was auricular flutter Although carotid sinus pressure will slow the ventricular rate it does not affect the auricular flutter itself and therefore is not of any value therapeutically even though it is a useful aid in diagnosis

CARDIAC ARREST

Stoppage of the heart is seen occasionally in the operating room Prompt and intelligent action on the part of the surgeon and the anesthetist may save the life of a patient whose heart has stopped completely Since the cause of cardiac arrest is usually ventricular fibrillation it is necessary to defibrillate the heart first The technic advocated by Beck is as follows Inject 5 cc of 2 per cent procaine hydrochloride into the right side of the heart followed by a brief period of cardiac massage to distribute the drug through the myocardial bed The heart is then placed between two large electrodes and an ordinary 110 volt A C current with 1 5 amperes is momentarily impressed through the heart between the electrodes Usually a series of such shocks is necessary to accomplish defibrillation If the treatment is successful, the ventricles cease fibrillating and remain in standstill momentarily before a supraventricular rhythm is established Massage is continued until the vigor of the heart is sufficient to empty the cardiac cavities

It is important to begin treatment immediately because if effective cardiac output has not occurred for over eight minutes the brain cells are probably permanently injured by the prolonged anoxemia

To prevent the occurrence of ventricular fibrillation at operation pre medication with procaine amide is often used especially if the anesthetic is cyclopropane and if epinephrine is to be given during the operation Procaine amide can be given orally (0 5 Gm every four hours)

STOKES ADAMS SYNDROME

This name is applied to the period of unconsciousness that is apt to occur in a patient with complete heart block This syndrome is noted either when the heart rate falls below a critical level (usually around 25 per minute) or when a prolonged period of asystole occurs The treatment is essentially an attempt to increase the ventricular rate This cannot be done by the use of atropine because this drug is ineffective below the auriculoventricular node in the heart Therefore, the therapeutic measures are concerned with either stimulating the ventricular muscle directly as with barium chloride, or with stimulating the

cedure is usually not popular with the patient

"Mecholyl by subcutaneous injection is most effective in the acute attack A dose not exceeding 25 mg should be injected subcutaneously, never intramuscularly If this is not effective, the dose may be increased by increments of 10 mg every fifteen minutes until the attack terminates The maximum dose is 50 mg Applying carotid sinus pressure immediately after injection will tend to amplify the effect of the mecholyl A syringe containing one mg of atropine should be ready for injection if the effect of the mecholyl is too violent Since mecholyl has such a powerful action, great care must be exercised in its administration

To prevent the recurrence of attacks of paroxysmal tachycardia the daily use of quinidine in small doses such as 0 2 Gm three times daily is often sufficient However, occasionally even larger doses of quinidine are unable to prevent attacks In that case, the patient should be digitalized and kept on a daily maintenance dose of digitalis If the attacks are mild and occur infrequently, it is usually not advisable to try to prevent the attacks by medication An attempt should be made to learn if there is any precipitating factor, such as overeating excessive use of alcohol or excessive mental strain Occasionally the attack appears to be on an allergic basis

VENTRICULAR TACHYCARDIA

The warning sign of impending ventricular tachycardia in a patient with coronary artery thrombosis is the presence of ventricular premature contractions Such a patient should be given a sufficient amount of quinidine to prevent the premature contractions otherwise ventricular tachycardia may occur Any patient on digitalis medication who develops premature beats should immediately cease taking digitalis even though proof may be lacking that the premature beats are due to digitalis This is important because sometimes the irregularity is the first sign of toxicity Quinidine is usually not effective in digitalis toxicity The administration of potassium salts by mouth may be of some value

When ventricular tachycardia is actually present, large doses of quinidine by mouth may be given depending on the tolerance of the patient Usually 0 4 Gm every three hours is a fairly effective dose Quinidine can also be given intravenously, but by that route it is not entirely free from danger A number of deaths have been reported from quinidine used intravenously Procaine amide is the most effective drug when used intravenously to stop ventricular tachycardia even when caused by digitalis toxicity The usual dose is 0 5 Gm administered slowly, although doses up to 1 Gm have been used It is especially valuable when this cardiac irregularity occurs during the course of an operation

AURICULAR FIBRILLATION

This irregularity in its chronic form is the most common of all in patients in the later phases of heart disease The problem here is to control the ventricular rate by increasing the degree of block in the auriculoventricular node The auricular rate in auricular fibrillation is usually over 400 per minute The ventricles do not respond to every auricular beat, so there is some degree of block even without digitalis Digitalis increases the block so that a ventricular rate of about 70 per minute can usually be obtained on an adequate digitalis maintenance dose

In the paroxysmal form of auricular fibrillation, the treatment is similar to that of paroxysmal tachycardia Paroxysmal auricular fibrillation is not necessarily associated with structural disease of the heart The use of digitalis during the attack probably will slow the ventricular rate but it may tend to prolong the attack An attempt

11. Vascular Diseases

I. Diseases of Arteries and Arterioles

CHARLES D. MARPLE
& IRVING S. WRIGHT

MANY diseases of the blood vessels are systemic diseases and involve the blood vessels of the viscera as well as those of the extremities Others are confined largely to the extremities and may be designated properly as peripheral vascular diseases

The responses of the smaller blood vessels to metabolic emotional and environmental changes control the peripheral blood flow Unfortunately knowledge concerning the physiology and functional pathology of these vessels is limited The treatment of diseases of these vessels is often empirical and sometimes unsatisfactory

Because the management of any vascular condition depends upon an accurate diagnosis and evaluation, the vascular history and physical examination must be methodical and painstaking The special form used for recording findings in the vascular clinic of the New York Hospital serves as an adequate guide (Table 9) A list of bedside examinations and tests is given in Table 10 and of procedures employed in the study of patients with vascular diseases but requiring special instruments or technics is provided in Table 11

Functional (Vasomotor) Conditions (Vasoconstrictor)

RAYNAUD S SYNDROME

The most important factors in the medical management of Raynaud s syndrome are (1) reassurance of the patient so that he or she does not develop an anxiety state over his illness and (2) instructions as to the proper protection of the involved limbs against cold Surgical treatment by sympa

sympathetic nerve fibres Epinephrine by injection is effective, but its action is short lived Ephedrine sulfate (15–50 mg) three or four times a day will often prevent the Stokes Adams seizures However, ephedrine will produce considerable cerebral excitation so that it may be necessary to try other drugs Desoxyephedrine and amphetamine are among the many substitutes for ephedrine that have been tried with rather indifferent success Barium chloride given by mouth is absorbed from the gastrointestinal tract in such variable amounts that it is often impossible to work out a satisfactory dose for the patient

CAROTID SINUS SYNCOPE

This condition is often confused with the Stokes Adams syndrome However the mechanism is entirely different Normal sinus rhythm is present The difficulty is in the carotid sinus which has become too sensitive, so that even moderate stimulation, such as twisting the neck or wearing a stiff collar may by pressure on the carotid sinus produce a long enough period of cardiac asystole to cause complete unconsciousness Since strong afferent stimuli from any part of the body may increase the sensitivity of the carotid sinus attempts should be made to find disease elsewhere than in the carotid sinus and correct it A common source of trouble is gallbladder disease Increased carotid sinus sensitivity has also been reported with ninth nerve neuralgia and renal calculus

Atropine sulfate, 0.5 mg three times a day will help to some extent in decreasing carotid sinus sensitivity The patient should be advised to wear a soft collar at all times and to avoid sudden twisting of the neck In intractable cases operation can be performed If possible, the carotid sinus nerve is severed If this nerve cannot be found the plexus of nerves can be stripped from the carotid sinus Unfortunately, this latter operation does not effect a permanent cure

NEUROCIRCULATORY ASTHENIA AND OTHER PSYCHOGENIC DISORDERS WITH CARDIAC SYMPTOMS

Although neurocirculatory asthenia is usually grouped with diseases of the heart because the outstanding symptomatology is related to the heart, it properly belongs as far as treatment is concerned, in the field of psychiatry The patient lacks the fundamental ability to stand up under severe strain, particularly if the strain is a combined mental and physical one such as encountered in the armed forces during a war This condition is rarely seen during peacetime probably because these people have adjusted themselves to a station in life where they are not subjected to much strain The problem in treatment, then, is chiefly to find the proper niche for these individuals in society and to convince them that they should remain at that level The most difficult patients to handle in this group are those who believe that they have some serious organic heart disease If this conviction is strengthened by the receipt of a pension or disability benefits, it is almost impossible to rehabilitate them Each patient must be treated individually and usually by a physician with psychiatric training The longer treatment is delayed, the less chance there is of rehabilitation

Many patients go to the doctor complaining of chest pain and frequently insist that they must have heart disease A careful and *complete heart examination should be made in all these cases If heart disease is* not found, a reasonable explanation for the pain must be given to the patient, otherwise the patient is well on the way to becoming a cardiac neurotic, a condition which can be acquired easily these days when so much publicity is given to diseases of the heart *

* See also Chapter 25

TABLE 9 NEW YORK HOSPITAL VASCULAR CLINIC HISTORY FORM (*Continued*)

VII EXAMINATION OF EXTREMITIES
Skin changes (temperature on palpation)

Part	Effect of Elev	Effect of Depend	Color Changes Due to Cold	Trophic Changes	Gang	Edema	Fungus
R arm hand							
L arm hand							
R leg foot							
L leg foot							

VIII GENERAL VASCULAR EXAMINATION

Artery		Tortuosity	Visible Pulse	Palpable Pulse	Tension of Pulse	Nodulation
Temporal	R					
	L					
Brachial	R					
	L					
Radial	R					
	L					
Ulnar	R					
	L					
Femoral	R					
	L					
Popliteal	R					
	L					
Posttibial	R					
	L					
Dorsalis pedpedis	R					
	L					

FUNDUS R
L
VEINS (Describe)

TABLE 9 NEW YORK HOSPITAL VASCULAR CLINIC HISTORY FORM

VASCULAR HISTORY

NAME	SEX	M S W D	AGE
ADDRESS	RACE	OCCUPATION	
REFERRED BY		BIRTHPLACE	

I PRESENT COMPLAINTS (including duration precipitating factors like temperature or injury, progression previous therapy)

Enter appropriate descriptive word or phrase do not use check mark

Fatigue or claudication
- location______
- severity______
- progression______
- produced by______
- relieved by______
- effect of heat or cold______

Rest pain
- duration______
- location______
- severity______
- progression______
- relieved by______

Phlebitis
- location______
- duration______
- recurrence______

Varicose veins
- location______
- duration______
- previous therapy______

Lymphangitis
- location______
- duration______

Color changes in extremities
- at cardiac level______
- on elevation______
- on dependence______
- effect of cold______

Sensitivity to
- cold______
- heat______

Ulcers:
- dates______
- general appearance______
- location______
- duration______
- previous healing______
- previous therapy______

Skin and subcutaneous changes (pigmentation elasticity trophic or fibrotic changes coarseness, sweating)

II PERSONAL HISTORY

Occupation past and present
(possible industrial hazards)

Use of—
- a Tobacco (age of onset of use kind and amount)
- b Alcohol (duration kind and amount)
- c Others (arsenic ergot lead etc)

Exposure to unusual cold or dampness

Exposure to chemicals

Family history of vascular or other diseases

Pediatric history

III PAST HISTORY

Diseases (vascular cardiac diabetes or other metabolic dysfunctions infections allergies etc)

Operations

Frostbite or chilblains

Pregnancies

Venereal disease

Variations in weight

IV GENERAL SYMPTOMATOLOGY

V GENERAL PHYSICAL EXAMINATION — WEIGHT

B P R_____ L_____

VI ORTHOPEDIC STATUS

ished or absent response to all pressor stimuli The ideal dosage is that which produces flushing warming and increased pilomotor activity without the unfavorable side effects Priscoline may be administered intramuscularly or intravenously in doses of 25–75 mg four times a day and divided doses totaling as much as 0 2 Gm have been given within a period of four hours without untoward effect Grimson has stated that the results of priscoline therapy in Raynaud s disease are sufficiently encouraging that the drug is used in preference to sympathectomy unless the patient develops signs and symptoms of *toxicity or tolerance*

Dibenamine has not been used widely because it must be administered intravenously, has evoked unfavorable side reactions more commonly than have the other blocking agents and because priscoline appears to be relatively effective in those instances where such an agent is indicated

Estrogenic hormone therapy may be of value in instances where Raynaud s syndrome first appears during pregnancy, or where it is aggravated during the menstrual period or at the time of the menopause A number of observers have reported favorable responses when women were given estrogenic hormone parenterally This is less apt to be the result when the disease is advanced

Recently Berger and Wright have reported cases of Raynaud s syndrome associated with the hyperabduction syndrome Some patients lost the Raynaud s syndrome when the position of hyperabduction was abandoned either at work or at sleep

Anemia may contribute to the progression of Raynaud s syndrome and should be corrected by appropriate therapy in all instances

Sympathectomy

In mild and nonprogressive Raynaud s disease sympathectomy is not indicated and a conclusion regarding the severity of such a case should not be drawn until the patient has been observed over a period of months and preferably through a complete cycle of the seasons We have observed patients who have shown no progression over periods of ten or twenty years When Raynaud s syndrome is progressive during each winter one may expect that the patient will have increasingly severe and more frequent attacks and that eventually a certain proportion of these patients will develop trophic changes and scleroderma Under such circumstances sympathectomy is justified both to decrease disability during the *cold seasons and to prevent the development* of ulceration and scleroderma

Preparation for Sympathectomy In the moderately advanced stage of the disease uncomplicated by scleroderma or trophic changes it is advisable for the patient to try if possible a season or two in a warm climate before sympathectomy is decided upon Such a patient may live comfortably in a mild climate and if this is possible economically it may obviate the necessity for operation In instances of the disease in which superficial ulceration has developed on the tips of the digits sympathectomy may be expected to speed the healing of the lesions and to relieve the pain It may not however prevent the recurrence of trophic lesions and the progression of scleroderma In selecting patients for sympathectomy the various tests which have been proposed such as the use of sympathetic blocking agents or paravertebral sympathetic block with procaine are not completely reliable indications of the ultimate value of sympathectomy It is probably advisable to perform them as crude prognostic guides but sympathectomy should not be withheld from a patient because the tests do not indicate a favorable response *

Sympathectomy for Raynaud s syndrome affecting the *lower extremities* is almost always satisfactory but one cannot predict

* See also Chapter 15

TABLE 9 (*Continued*)

IX OSCILLOMETRY

Maximum Readings	Right	Left
Foot		
Above ankle		
Below knee		
Above knee		
Hand		
Above wrist		
Below elbow		
Above elbow		

X OTHER TESTS—Allen test—enter P for patent O for occluded

	Right	Left
Radial		
Ulnar		

XI SUMMARY AND CONCLUSIONS (Resume of history physical findings special tests and laboratory procedures *Indicate* provisional diagnosis further tests emergency treatment and suggested course of therapy)

thectomy remains the most satisfactory method of treating those instances of Raynaud s syndrome which do not respond to medical management

Psychotherapy

Because many of the patients who suffer from Raynaud s syndrome have unstable vasomotor systems they are prone to develop severe anxiety over the possibility that their disease may lead to the loss of digits or of limbs It is imperative that the attending physician reassure the patient on this point In some instances there has been excellent subjective and some objective response to psychotherapeutic management Psychiatric study of the patient to correct emotional instability is an important aspect of the treatment of Raynaud s syndrome It should be emphasized to the patient that the disease may become even more disturbing than at the time of the initial consultation and that sympathectomy may be necessary Sympathectomy will frequently relieve symptoms which have become progressively worse

Protection Against Cold

The patient with Raynaud s syndrome must be protected carefully against cold Ideally he should reside in a warm climate particularly during the winter months This is impossible for many patients Furthermore residence in a warm climate will not control the condition if emotional disturbances and other contributory factors persist Outdoor work and sports during the winter must be avoided If the patient must remain outdoors during cold weather, warm clothing is absolutely essential Shoes should be sufficiently large to permit the patient to wear one or even two pairs of

The *indications* for which sympathectomy may be considered are (1) minimal and slowly progressive acroscleroderma with associated Raynaud s phenomenon of moderate degree (2) moderate acroscleroderma with frequent attacks of severe pain in the fingers resulting from vasospasm and (3) mild to moderately severe sclerodactylia with recurrent painful ulcers or fissures which do not respond to more conservative measures

ACTH and Cortisone

As one of the so-called collagen diseases early scleroderma might be expected to respond to therapy with ACTH or cortisone However, scleroderma exhibits a relatively small element of acute inflammatory reaction and a large element of fibroblastic proliferation and formation of collagen Diagnosis is rarely established until a considerable degree of collagen formation has occurred A priori one would *not expect any* substantial response to this type of therapy in most instances

Experience to date with long standing *cases of scleroderma* tends to confirm this view Inhibition of fibroblastic proliferation and of collagen formation has not been *striking* Theoretically intensive therapy during the early stages and prolonged maintenance therapy should reverse acute sclero*derma* and maintain a state of remission but experience in this connection has not *come to our* attention In our experience cases of a type suitable for ACTH and cortisone are exceedingly rare

ACROCYANOSIS

Ordinarily acrocyanosis is a completely innocuous condition and nothing is necessary in the way of treatment other than to protect the patient against the cold The patient should be kept active physically and mental strain should be reduced to a minimum Psychiatric advice should be obtained when necessary The basal metabolic rate should be determined and thyroid administered if it is low The use of mecholyl iontophoresis has been advocated *but* usually is not effective In the uncommon severe case a sympathectomy may be performed with the prospect that the results will be as good or better than that obtained in Raynaud s syndrome

VASOSPASM

Vasospasm is the natural response of the blood vessels to trauma which directly or indirectly affects the vascular system Depending on a number of factors it may involve *only a relatively short segment of* a single vessel may spread to neighboring vessels or may become so generalized as to involve an entire limb or a great portion of the body Possibly this vascular response to trauma is compensatory in purpose Ordinarily, however, its persistence is actually harmful This is particularly true when in traumatic injuries to the limbs or in occlusions of the *major* arteries the impaired vitality of the tissues is aggravated by the ischemia of widespread vasospasm In all instances of traumatic and occlusive impairment of the circulation the role of vasospasm must be evaluated promptly and measures for its relief applied immediately The life of a limb may depend upon the prompt relief of vasospasm

Symptoms and signs of arterial insufficiency, presumed to be the result of occlusion or of loss of continuity, may disappear with the relief of the associated vasospasm

Treatment

Treatment of vasospasm involves an attempt to combat vasoconstriction and to produce maximum vasodilatation in the areas involved The affected limb should

to it directly since overheating increases the metabolic demands of the tissues and

with certainty the benefit which will be obtained from the various methods of interrupting the sympathetic nerve pathways to the upper extremities Technically speaking, the surgical procedure of choice includes both sympathetic ganglionectomy and resection of the sympathetic trunk In far advanced cases complicated by scleroderma, the results are rarely favorable

The late results of sympathectomy for Raynaud s syndrome will depend upon the completeness of the operation, the stage of the disease in which the operation is performed and, perhaps, on the sympathetic parasympathetic balance in the particular patient

No conclusion should be drawn regarding the clinical results until the patient has been followed for at least one and preferably two or three years postoperatively There is often an improvement for some months postoperatively, with encouraging changes in the surface temperature and a relief of symptoms but the results in the same patient at the end of one, two or three years may be entirely unsatisfactory In some instances ulcers will have developed and the disease will be manifestly progressive

SCLERODERMA

Treatment of scleroderma of any type has been uniformly unsuccessful Palliative measures including the protection of the diseased areas against trauma and extreme changes of environmental temperature increase of the peripheral circulation, and maintenance of suppleness of the skin of the extremity have been of considerable value in affording the patient symptomatic relief and in slowing the progress of the disease

The patient with scleroderma should reside in a warm, dry climate when possible If he is unable to do this every effort must be made to avoid exposure to dampness and to cold The hands in particular, must be protected carefully Washing dishes in cold, or in cool water, or with strong soaps is inadvisable Any irritation or trauma which may produce fissures in the sclerodermatous skin may result in a painful lesion Stubborn infections may complicate relatively minor lesions and lead eventually to the loss of a digit

As in the presence of any peripheral vascular disease, cutting of the nails and trimming of corns and callosities must be done with the greatest care A change of occupation may be advisable if the patient's hands are subjected to such trauma as that involved in typing or in using machine tools

Any measure which will increase the peripheral circulation temporarily or permanently is of value in those patients who present a considerable degree of vasospasm Such treatment must be instituted early since the sclerodermatous changes are both resistant to therapy and insidiously progressive When Raynaud s phenomenon is associated with painful ulcerations on the extremities measures which produce even temporary vasodilatation may be of some benefit particularly the use of the blocking agents, warm baths, and the intravenous injection of foreign proteins (typhoid vaccine)

Sympathectomy

Sympathectomy has been of limited value in treating scleroderma In advanced cases it is not effective and in the slowly progressive types of acroscleroderma it cannot be depended upon to produce more than temporary improvement Following sympathectomy there is often an increase in the skin temperature, a diminution of subjective symptoms, and, more rarely, a softening of the skin There may be a temporary decrease in the rate with which the scleroderma progresses Superficial ulcers and fissures often heal rapidly Thus, the early results of sympathectomy are often good even though the late results are ordinarily disappointing

Following aspiration to be certain that the needle is not within a vessel or the sub arachnoid space, 5 cc of a 1 per cent solu tion of procaine is injected through each needle A satisfactory injection is mani fested within a few minutes by the warming and drying of the skin over the affected limb and by the increased prominence of the superficial veins The pulsations of peripheral vessels previously absent or feeble may return or become stronger

Stellate Ganglion Block Stellate gang lion block is performed in instances where the upper extremity is involved This may be done by an approach similar to that described above for lumbar block and with the patient in the prone position Injection is then made at the levels of the spinous processes of the first three thoracic verte brae It may be done also by an anterior approach with the patient seated or in the supine position In the latter approach an intracutaneous wheal of procaine is made in the skin immediately over the upper border of the clavicle 1 cm medial to its midpoint A fine lumbar puncture needle is introduced perpendicular to the clavicle and is directed posteriorly and medially at an angle of 45 degrees with the midline The point of the needle, after being intro duced for a distance of 6–7 cm, impinges against the anterolateral surface of the body of the seventh cervical vertebra or at the junction between the seventh cervical and first thoracic vertebrae, where the stel late ganglion lies After ascertaining by aspiration that the needle is not in a vessel 10 cc of 1 per cent procaine solution is introduced A satisfactory injection pro duces a Horner s syndrome and warmness and dryness of the hand, arm, neck and face on the affected side

Neurovascular Syndromes of the Shoulder Girdle

CERVICAL RIB AND SCALENUS ANTICUS SYNDROMES

Many persons who have cervical ribs are never aware of this fact Treatment is neces sary only when symptoms are produced by compression of the subclavian vessels and brachial plexus by the scalenus anticus *muscle and this may occur in the presence* or in the absence of a cervical rib When the symptoms are mild conservative meas ures may benefit or completely relieve the patient Obese patients should reduce their weight to reduce the amount of fat in the supraclavicular fossa and to lessen the load on the shoulder girdle

The application of *heat locally* and the use of *analgesic drugs* such as acetylsalicylic acid is often of considerable benefit Sleep ing with the arms in a position found by experience to afford the greatest comfort may bring about much symptomatic im provement

When surgical intervention is necessary because of severe pain, paresthesia, circula tory disturbances with or without gangrene and/or muscular atrophy, anterior scale notomy is ordinarily satisfactory Cervical *sympathetic* ganglionectomy is advisable when symptoms of vasospasm persist It is not usually necessary to remove the cervical rib

COSTOCLAVICULAR SYNDROME

This syndrome, first described by Fal coner and Weddell in 1943 is produced by holding the shoulders backward and down ward or by hyperextending the neck These movements produce pressure upon the subclavian vessels and upon the nerves of the brachial plexus as they pass between

may produce burns Vasodilatation in the involved limb will be obtained as far as possible by the application of heat to the trunk (reflex heat) by means of an electric heater, lamp or pad or by other heating devices Whiskey or brandy in amounts of one and one half to three ounces may be given every four to six hours and papaverine hydrochloride should be given by intravenous injection in amounts of 0 06 0 12 Gm every four hours

Papaverine The intra arterial injection of papaverine into the major artery of the affected limb is often even more effective The technic for intra arterial injection is as follows 0 06 Gm of papaverine hydrochloride is dissolved in 5 cc of distilled water and is drawn into a 5 cc syringe to which a 20 gauge needle 2 inches long is attached The artery is located by its pulsations and is fixed between the second and third fingers of the left hand The needle is guided directly into it as one would do a venipuncture Entrance into the artery is recognized by a pulsating surge of bright red blood into the syringe The solution is injected slowly into the artery the needle withdrawn and firm pressure applied to the puncture site for three to four minutes The effects of vasodilation are noted within five to ten minutes and extend peripherally to the most distal point of adequate circulation

Tetraethylammonium Chloride Tetraethylammonium chloride or bromide may be given intramuscularly in doses of 0 3–0 5 Gm (300–500 cc) every four to six hours but the results in our hands have not been striking and the risk of producing serious hypotension probably outweighs the potential value of this agent We would prefer to give priscoline in doses of 50 mg intramuscularly repeating the injection at intervals of two to six hours depending upon the degree and duration of response to the drug Following relief of vasospasm priscoline may be continued orally

Paravertebral Block As might be anticipated from the seriousness and persistence of the precipitating factor in vasospasm, whether it be trauma or vascular occlusion the relatively simple emergency measures described above do not produce relief in all instances One should then consider the use of a procaine paravertebral block which when employed promptly, will almost always produce temporary improvement for a period of from several hours to as long as two to three days Paravertebral block should be repeated as often as necessary as long as each block produces an improvement in the affected limb

When there is no response to a single or once repeated block sympathetic ganglionectomy should be considered One must be certain, however, that failure of the sympathetic block is not due to the failure to inject all of the sympathetic nerves to the involved area or that the failure of the local circulation to improve is not due to an organic cause rather than to vasospasm

A *lumbar sympathetic block* is performed on the affected side with the patient lying either in the lateral recumbent position, or in the prone position with a pillow under the lower abdomen The cutaneous sites of puncture are determined by marking a series of points about two and one half to three fingerbreadths lateral to and on a horizontal level with the spinous processes of the first four lumbar vertebrae An 80 mm needle is inserted perpendicular to the skin at each point until it reaches the transverse process of the vertebra The direction of the needle is then changed slightly and it is passed inward and either above or below the transverse process until it comes into contact with the vertebral body The bevel is turned toward the bony surface so that the sensation produced by the slight scraping of the needle against the surface of the vertebral body can be felt When this sensation is lost the tip of the needle is in close proximity to the sympathetic trunk

litions of solution of epinephrine hydrochloride have been reported as successful

Some symptomatic relief may be obtained by avoiding all conditions and circumstances which may produce vasodilatation. The patient may obtain relief by moving to a climate where temperatures are moderate. He should avoid exposing his feet to warmth such as that produced by wearing heavy socks or sitting near a stove, a fireplace or a heater. The use of light weight socks or stockings and of sandals or perforated shoes may be helpful.

When all of these measures have failed to produce relief, it may be necessary to anesthetize the skin of the feet by *cutting or crushing the peripheral nerves* distributed to the areas most productive of distress. Unfortunately, the numbness and paresthesia resulting from destruction of peripheral nerves may be as disturbing to the patient as was his erythromelalgia.

Organic (Structural) Conditions: The Occlusive Arterial Diseases

ARTERIOSCLEROSIS OBLITERANS

The treatment of arteriosclerosis of the peripheral vessels will vary considerably depending upon the degree of involvement and the symptoms which have arisen.

General Considerations

It is important to instruct patients with arteriosclerosis obliterans as to the slowly progressive nature of the disease, the proper care of the feet and the need for protecting the feet and legs from all types of injury. This is vital when the coexistence of diabetes mellitus of polycythemia or of other chronic degenerative or metabolic disease predisposes the arteriosclerotic patient to serious complications and an unfavorable outcome. Patients with arteriosclerosis obliterans who are obese should reduce their weight. If their blood serum contains a high concentration of lipids (lipemia) they should be placed on a diet low in fat and in cholesterol. If they are diabetic their diabetes should be controlled carefully and the patient should receive painstaking instructions regarding the care both of his diabetes and of his general health.

Tobacco. Patients with obliterative disease of the peripheral vessels must eschew the use of tobacco. Smoking reduces the blood supply to the extremities by producing vasospasm whether the vascular system is normal or diseased. Even though vessels exhibiting advanced sclerosis may be unable to constrict, the collateral circulation upon which the integrity of the limb may depend can be seriously impaired by the vasospastic effects of smoking.

Hygiene. Cleanliness of the feet is of the utmost importance because of the ease with which the patient with impaired circulation can develop an infection. The feet should be bathed each day in water which is comfortably warm, using a bland facial type of soap. Drying of the feet should be done meticulously after bathing, with particular attention to the spaces between the toes. After drying the feet, they should be anointed lightly with lanolin or baby oil to prevent maceration and cracking. Toenails should be kept trimmed carefully and where obesity or incapacity prevents the patient from doing this conveniently, some other member of the family, a podiatrist or the physician should perform this necessary duty. Socks should be changed daily and rinsed out between each wearing. Shoes must be comfortable and well fitted to the feet.

the anterior surface of the first rib and the posterior surface of the clavicle The syndrome is seen commonly in soldiers who are forced to stand for long periods of time while carrying heavy packs The forcing backward and downward of the shoulders will obliterate the radial pulses in a high percentage of persons In most persons, avoiding this position by avoiding the lifting and carrying of heavy weights will give complete and permanent relief

For the majority of persons developing this syndrome the strengthening of the muscles of the shoulder girdle and the progressive stretching of the nerve trunks and blood vessels by exercise will produce improvement

Paull has recommended the following technic The patient suspends himself from a bar with his hands held in close approximation and the muscles of the shoulder girdle relaxed This is done three or four times a day for as long a period of time as comfort permits To build up the muscles antagonistic to those which are being stretched the patient should also shrug his shoulders many times each day while standing erect and holding a 10–20 lb weight in each hand

In severe cases unrelieved by these measures, surgical section or removal of the first rib, or grooving of the anterior surface of the first rib may be considered

HYPERABDUCTION SYNDROME

The neurovascular syndrome produced by hyperabduction includes the development of paresthesias and of numbness and tingling in the hands and arms after sleeping with the arms brought together above the head Atrophy may occur occasionally, gangrene rarely The syndrome may occur also in those whose occupation causes them to work for prolonged periods with their arms in the hyperabducted position, as, for example, painters who work on ceilings, riveters who work overhead, and garage mechanics who work in 'pits When the syndrome develops, it is generally possible to demonstrate the obliteration of the pulse when the arms are hyperabducted In an occasional patient, a mixed syndrome, including the features of the scalenus anticus syndrome as well as those of the hyperabduction syndrome may be demonstrated.

Treatment of the hyperabduction syndrome is in most instances simple and highly satisfactory The patient must avoid sleeping and working with his arms in the position of hyperabduction

A change of occupation may be necessary Patients who have suffered fractures or other injuries to the arm which necessitate splinting or casting in the position of hyperabduction may develop this syndrome Relief is afforded by modifying the position of immobilization

Functional (Vasomotor) Conditions (Vasodilator)

ERYTHROMELALGIA (ERYTHRALGIA)

The treatment of erythromelalgia is not uniformly successful When the condition arises secondarily to some other disease, usually a vascular disease such as hypertension or thromboangiitis obliterans, an organic neurologic disease, polycythemia, gout, or heavy metal poisoning by thallium, mercury, or arsenic, the treatment of the primary disease is essential to the successful management of the erythromelalgia

Acetylsalicylic acid in doses as small as 0 65 Gm may provide a surprising amount of relief and this relief may persist for several days at a time Injections or inha

may be at a higher level, they induce metabolic stimulation to which the vessels may be unable to respond already damaged vessels *may be forced into sudden vasospasm* by the sudden change in temperature and considerable pain *may be experienced dur ing* the cold phase to treatment

Whirlpool baths are useful if the temperature of the water is maintained at a suitable level There does not appear to be any great advantage to this type of bath which has the serious disadvantage of being available ordinarily only in hospitals equipped with departments of physiotherapy

Finally, affected limbs may be bathed by *the use of wet dressings The tendency of* these to cool under the most favorable circumstances and by cooling to produce vasoconstriction is a serious disadvantage Moist soaks for fifteen to thirty minutes once or twice a day are preferred to continuous wet dressings They must be applied carefully and attended closely The affected limb must be dried carefully and anointed after each soaking

Exercise Postural exercises first suggested by Buerger *and modified by* A W Allen, are prescribed in most instances *They are performed* as follows

Position 1 while lying on his back the patient rests *his legs on an inclined* plane raised to an angle of 30°–45° until the skin of the feet is completely blanched

Position 2 the patient sits with the legs hanging over the edge of the bed and the feet and toes are put through *a series of* motions the ankle is flexed upward and downward, the foot is turned inward and outward and the toes are spread and closed These exercises are continued until the maximum rubor is attained

Position 3 the patient lies supine in bed *with the legs horizontal* for five minutes wrapped in a woolen blanket and warmed by a hot water bottle or electric pad The patient performs about one half dozen exercises on two occasions each day

Postural exercises may be applied to the passive patient by placing *him* upon a *Sanders oscillating bed* This bed tips on a transverse axis so that the ends of the bed are alternately raised and lowered through *an arc of* approximately 60 degrees. The speed of oscillation can be regulated so that *a cycle is completed in from two* to seven minutes Postural exercises can be carried out rhythmically *and for long periods of* time without effort by the patient on this bed Furthermore, the entire body *partic ipates* in the changes of posture Other therapeutic measures may be applied to the patient without interrupting the postural *exercise The disadvantage of the bed* is its cost and the fact that it often is not readily available

Heat The application of heat, when done properly, is indicated in mild instances of obliterative vascular disease Temperatures above 95° F should never be applied directly to the hands and feet The temperature of the limb must never be elevated beyond the point to which its circulation can adjust to metabolic demands *Reflex heat, obtained by applying such* forms of heat as an electric pad, a heating lamp or a well covered hot water bottle to the abdomen or to the sacral area often gives a significant measure of symptomatic relief

Sympathectomy Sympathetic blocks *are not usually indicated* in this type of patient as they must be repeated frequently and under hospital conditions Sympathectomy is not indicated ordinarily while periarterial sympathectomy *has been largely* abandoned Peripheral sympathectomy by crushing *alcohol injection or section* of the mixed nerves is recommended only for *patients who suffer* intractable pain and has the disadvantage of being followed by disturbance of sensation over the distribution of the treated nerves

Patients Who Exhibit Intermittent Claudication Only

In those instances of arteriosclerosis obliterans in which the only symptom is intermittent claudication and in which there is no rest pain neuritis ulceration, or gangrene it is unnecessary to place the patient at continual bedrest in the hospital or at home It is desirable that the head of the patient s bed be elevated so that the lower limbs are at least six inches below the level of the heart This is done by placing six inch blocks underneath the legs at the head end of the bed not by propping the patient up with pillows The majority of patients become reconciled quickly to the unusual position and are not inconvenienced or annoyed by it

We prescribe *whiskey or brandy* routinely in doses determined by the patient s tolerance to alcohol and by the degree of vasodilatation obtained Ordinarily 1 1½ oz of whiskey or brandy once or twice a day is satisfactory In diabetics who are on a carefully balanced regimen the alcohol intake must be considered in calculating the dietary and insulin requirements

Drug Therapy A large number of drugs have been advocated for the treatment of arteriosclerosis obliterans Those which have been recommended for reputed vasodilator properties include the nitrites and related compounds the methylxanthines the cholinergic drugs and papaverine None of these drugs is effective in any significant number of patients It is possible that papaverine hydrochloride may be more effective than has been demonstrated hitherto if it is given in somewhat larger doses than has been customary perhaps in amounts of 0 2 Gm orally every four hours In our experience doses of 0 1 Gm every four hours have not been as effective as is the administration of alcohol orally

The *sympatholytic and adrenolytic drugs* may be useful in improving the blood supply to the affected extremities Although the impaired circulation is the result of an obliterative process and the sclerotic major arteries cannot be expected to respond in any considerable degree to vasodilator drugs, a collateral circulation usually develops as the circulation through the usual channels is progressively impaired The integrity of a limb whose major vessels are seriously obstructed by arteriosclerosis obliterans may depend upon the adequacy of the blood supply through these collateral channels The sympatholytic or adrenolytic agents are used to relieve reflex vasospasm and to produce vasodilatation in these collateral vessels

Tetraethylammonium chloride (etamon) may be given in doses of 0 3–0 5 Gm (3 0–5 0 cc) intramuscularly at intervals of from once a day to two or three times a week or priscoline may be injected in doses of 50–75 mg intramuscularly at similar intervals, or may be given in doses of 50 mg orally three or four times a day

Baths There are several types of baths which are used to warm the affected limb and to improve the circulation The first of these is the *modified sitz bath* which can be used if there are no open lesions on the limbs The patient is instructed to sit in a bathtub containing approximately 18 inches of water maintained at a temperature of approximately 95°–100° F (35°–38° C) for from twenty to thirty minutes once each day The temperature is maintained by adding hot water from time to time The heated water extends high enough on the body to influence the collateral vessels in the trunk and thighs If the temperature of the water produces discomfort it should be reduced by several degrees

The *contrast bath* has decreased in popularity during recent years because of several objections These baths cannot be applied ordinarily to a level higher than the knees while the arterial obstruction

the optimum line of demarcation established Amputation of the toes should be done at the base of the toes when possible and this depends upon the adequacy of the circulation at this level Amputation should not be done until intensive medical management has been carried out for a period of time sufficient to control infection and to insure the best possible result Amputation may be necessary at a higher level if gangrene spreads or if pain is excessive and not otherwise controllable In those instances where gangrene spreads up the foot and into the leg amputation must be performed at the level indicated by the spread of the process If oscillometric readings are essentially absent below the knee amputation should probably be performed just above or just below the knee joint

Use of Anticoagulants

The use of the anticoagulants in arteriosclerosis obliterans has not been explored fully The value of heparin and 'dicumarol in coronary occlusion with myocardial infarction and in acute arterial occlusions suggests that these agents may have considerable value in selected cases of arteriosclerosis obliterans They are probably indicated in all instances of sudden arterial occlusion Whether or not they are indicated in instances of arteriosclerosis obliterans uncomplicated by gangrene or arterial occlusion is not yet known *

Our experience suggests that refrigeration is not ordinarily of value in the preservation of a limb in which the circulation is seriously impaired If amputation is to be performed refrigeration anesthesia may be helpful This is particularly true in the presence of active infection or in patients who are aged debilitated or suffering from uncontrollable diabetes mellitus

* See also Chapter 13

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

General Considerations

All patients who suffer from thromboangiitis obliterans must abstain totally and permanently from the use of *tobacco* It is now recognized that those patients who give up tobacco at an early stage of their disease stand an excellent chance that the disease will be arrested at that particular stage Experience demonstrates forcibly that those who do not give up tobacco progress inevitably to a more serious state There must be no equivocation by the physician or patient on this point

These patients must be instructed concerning the nature of their disease and its manifestations since they are, as a rule young or middle aged and anticipate many years of life The consequences of their illness are of considerable social and economic importance to themselves to their families and to society

Patients with Buerger's disease must be instructed to care for their hands and feet They must be cautioned to avoid mechanical thermal and chemical trauma They must watch for and attempt to prevent the development of epidermophytosis They must keep their hands and feet scrupulously clean and must anoint their extremities with lanolin or with baby oil following bathing and washing to prevent maceration They must trim their nails carefully and wear well fitted shoes free of protruding nails They must avoid minor trauma to the limbs which might be immaterial to the normal person but which may lead to infection gangrene and to the loss of the limb in the person with grossly impaired circulation

Patients with Intermittent Claudication and Mild Arterial Insufficiency Only

In such patients the elevation of the head of the bed at home the ingestion of alcohol once or twice a day and general

Patients Who Suffer Rest Pain or Ischemic Neuritis, but Who Do Not Have Gangrene or Ulceration

These patients should be hospitalized, if this is possible, or kept at rest in bed at home until their pain is controlled A Sanders oscillating bed should be used if it is available, if not, the head of the bed should be elevated at least 6 inches on wooden blocks Pain is controlled both by the use of appropriate sedatives or opiates and by the use of all measures designed to improve the circulation to the affected limb —alcohol by mouth, reflex heat, or priscoline' by mouth or by injection The use of normal or hypertonic saline solution intravenously has not been of any value in our hands The use of the vasodilator drugs already deprecated, may be tried systematically as they are sometimes effective in an individual patient The use of histidine and ascorbic acid as advocated by Wirtschafter and Widmann has not been satisfactory in our hands The use of ether intravenously as described by Katz of New Orleans and more recently by Williams may be of value for the relief of pain, but clinical improvement following its use has not been impressive in our experience

If pain continues after a fair trial of these medical measures, sympathetic blocks may be done and consideration given to the performance of a lumbar sympathectomy

The injection of "carbogen' (5 per cent carbon dioxide and 95 per cent oxygen) subcutaneously has been advocated as a measure to increase the peripheral blood flow The gas is permitted to flow through sterile tubing into a 20 gauge needle which is inserted under the skin of the calf or of the forearm A sizeable bleb is formed within 15 or 20 seconds The gas can be dispersed by milking it up or down the limb One or two injections per week are recommended The results are not very striking

Patients With Ulcers or Superficial Gangrene

The procedures applied to patients with rest pain and neuritis should be applied as indicated to this class of patient In addition, warm saline soaks should be applied to the ulcers once or twice a day for the expressed purpose of removing eschar and debris Continued soaks are undesirable as they macerate the surrounding healthy tissue The bacterial flora of ulcerations should be reduced by the local application of antibiotics, in aqueous solution during the period of soaking and suspended in suitable ointment vehicles during the intervals between soaks The selection of an antibiotic should depend upon the demonstration of the specific organisms present in the lesion The sulfonamides penicillin streptomycin, or tyrothricin may be used When local infection has been adequately controlled the application of powdered red blood cells will frequently assist the healing of the lesion Sulfonamides or antibiotics may be given parenterally in those instances where there is evidence of systemic or spreading infection, or when local application fails to control the local infection

The healing of ulcers of the extremities depends primarily, as a rule, on the sufficiency of the circulation and it is to this

or to previous attacks of thrombophlebitis must be corrected by the appropriate measures discussed in a subsequent section of this chapter

Patients with Gangrene of the Toes, Osteomyelitis of the Toes, or Open Ulcers Implicating the Joints of the Toes

In these cases, the regimen previously outlined should be carried out with meticulous care If possible amputation should be delayed until the maximum amount of gangrenous tissue has sloughed out and

there is a marked vasomotor disturbance or Raynaud's phenomenon of the digits of the affected extremities

Patients Suffering From Minor Ulcerations, Gangrene, or Local Infection

These patients should be hospitalized in a warm room, preferably on a Sander's oscillating bed. A cradle should be used to keep the bed clothes from the affected limb, but a heat box is undesirable unless thermostatically controlled at 35° C. Typhoid vaccine, sympatholytic or adrenolytic drugs, sympathetic blocks, and sympathectomy should be utilized to produce the maximum improvement of the circulation. Locally, warm saline soaks (temperature of 35° C) for periods of thirty to sixty minutes two or three times a day are preferred to continuous wet packs.

Local infection must be controlled by the judicious use of sulfonamides or antibiotics applied locally or given systemically as indicated by the response of the infectious process. Again, the agent of choice depends upon the bacterial flora of the lesion. Powdered red blood cells often assist materially in speeding the healing of ulcerations. Chemotherapy by oral or by parenteral routes is generally not necessary unless systemic or spreading infection occurs.

Patients with Massive Gangrene of the Digits and Osteomyelitis

These patients should be managed conservatively until the optimum time for surgical intervention. If possible, necrotic tissue should be permitted to slough out spontaneously and healing permitted to occur at its own rate. When healing does not occur after a suitable period, surgical amputation must be considered.

When extensive gangrene involves the digits and the foot or the leg as well, *amputation* should be performed at an opportune moment and at the site of election. *Antibiotic therapy* should be used preoperatively and postoperatively. *Anticoagulant therapy* may be advisable, particularly postoperatively.

When there is early and extensive thrombophlebitis, which is not unusual, therapy should include management of the thrombophlebitis according to the plan outlined subsequently in this chapter.

When there is an acute arterial occlusion, a common complication which is usually progressive and extensive, the appropriate treatment must be applied promptly and energetically. The treatment is described in the following section of this chapter.

ACUTE ARTERIAL OCCLUSION (ARTERIAL THROMBOSIS AND EMBOLISM)

If nothing but the simplest conservative treatment is applied in instances of acute arterial occlusion, approximately 50 per cent of patients with such occlusions of major arteries of the extremities will develop gangrene. It is extremely important that the diagnosis of acute arterial occlusions be made promptly and that treatment be instituted at the earliest possible moment.

It is also important to determine immediately if the acute occlusion is due to an embolus. If it is, the physician must decide whether to attempt an *embolectomy*. If this operation is elected, each passing hour decreases the chances for its success. Embolectomy is performed less frequently since the introduction of anticoagulant therapy and of repeated sympathetic blocks, but under the favorable conditions of early operation by highly skilled surgical personnel, embolectomy may be the measure for saving a limb.

These patients should be hospitalized. They should be placed in bed in a warm room, at a temperature of 80°-85° F. Ideally the patient should be placed in a Sander's oscillating bed, set with the minimum low head and the maximum low foot

hygienic measures are usually sufficient to control the process if the patient abstains from smoking Postural exercises may be of value The patient should examine his limbs regularly and carefully for signs of progression of the disease or the intervention of complications He should report to his physician at frequent intervals so that the status of his peripheral circulation may be determined

Patients with Claudication Coldness of the Extremities and Rest Pain or Ischemic Neuritis, but without Ulceration or Gangrene

These patients should be hospitalized in a warm room until the symptoms are relieved The Sanders oscillating bed used for periods of eight hours a day is valuable in the treatment of thromboangiitis obliterans The patient's feet may be placed in a cradle but the use of heat is strongly condemned unless it is controlled thermostatically at a level not greater than 95° F (35° C)

Nonspecific Foreign Protein Therapy The value of nonspecific foreign protein therapy has been established at the Mayo Clinic and in our own experience Typhoid H antigen and a typhoid vaccine prepared especially for this purpose by a commercial laboratory have been used extensively with success It must be remembered that the vaccine is a suspension in which the suspended material tends to settle It will therefore vary in concentration unless shaken thoroughly before use

Typhoid vaccine diluted to 100 million organisms per cc is administered intravenously as follows The first doses consist of 5 million organisms injected every three days provided that the effect of the last previous dose has worn off completely The object is to elevate the patient's temperature by about 2°–3° F without producing a chill There may be a slight drop in the surface temperature of the body just prior to the elevation of the body temperature The surface temperature of the tips of the normal extremities rises from 4° to 6° F with the fever but the rise in surface temperature over the diseased limb will depend upon the degree of occlusion and the development of collateral circulation When 5 million organisms fail to produce a satisfactory rise in temperature the dose is increased to 8 to 10 million organisms and kept at this level as long as there is a satisfactory response Doses are increased thereafter in increments of 3 to 5 million organisms whenever the effect of a preceding dose is inadequate to produce the desired febrile response If the temperature rises above 103° F, or if a chill occurs the next dose is reduced by 2 to 3 million organisms In the majority of patients the peak dose appears to be in the range of 70 to 130 million organisms, a dosage level which may be continued indefinitely

Ordinarily such treatment is continued for two or three months A rest period of similar duration may be followed by a subsequent course of therapy We have not encountered any serious side reactions which could be attributed to this therapy with certainty but we suspend therapy during the course of any intercurrent infection or other serious illness This type of therapy has been extremely gratifying in patients with ulcerations Ulcers appear to heal more rapidly and there is a considerable relief of pain There does not seem to be any influence on intermittent claudication

Sympathetic Block If the use of alcohol by mouth analgesics and hypnotics and the administration of typhoid vaccine fail to produce satisfactory results, recourse may be had to the blocking of the sympathetic pathways by the use of sympatholytic or adrenolytic drugs or by paravertebral block Irrespective of the results of these temporary measures sympathectomy should be considered in those instances where

and to prevent further embolization The administration of an anticoagulant should be begun immediately after diagnosis If surgery is being considered, it is possible to delay anticoagulant therapy briefly, but, if there is a delay before surgery, anticoagulants should be given during this interval Embolectomy is now largely confined to emboli lodged at the bifurcation of the aorta or the femoral arteries If this is to be attempted it is well to do it at the earliest possible moment, preferably not later than twelve hours after the embolic episode Anticoagulants must be used with skill and caution after such surgery The anticoagulant effect may be antagonized by proper measures prior to surgery

Heparin is the drug of choice for the immediate treatment of an acute arterial occlusion because of its prompt action The first dose should be administered by intravenous injection, but subsequent doses may be given by intermittent subcutaneous or intramuscular injection *Dicumarol* may be started immediately with the administration of 0 3 Gm orally on the first day, later doses being guided by the extent to which the prothrombin time is prolonged on subsequent days Heparin may be discontinued when the patient is under the full therapeutic effect of the 'dicumarol

The use of the anticoagulants does not relieve the physician from the responsibility of determining the cause and source of the acute arterial occlusion For example, in instances of rheumatic heart disease with auricular fibrillation, the source of emboli to the peripheral vessels is a mural thrombus in the left auricle or ventricle of the heart This is an indication for maintaining the patient on anticoagulant therapy preferably with dicumarol, for months or even years

The patient remains in the hospital at rest in bed and in a warm room until the circulation has re established itself A Sander s bed if available, is used for a period of eight hours a day or more Alcohol is continued for its vasodilating effect Sedatives are administered as necessary Sympathectomy may be undertaken in selected cases

If *gangrene* develops penicillin or a sulfonamide is applied locally—in the form of an ointment, solution or powder—and parenterally, for the control of infection At the most suitable time according to the judgment of the surgical staff, amputation may be performed

TEMPORAL ARTERITIS (CRANIAL ARTERITIS)

Cases of cranial or temporal arteritis may undergo a complete remission of symptoms without any treatment Excision of the involved temporal vessels frequently produces dramatic relief from pain, but this is not always so, probably due to the involvement of deeper lying vessels Intracranial involvement has been demonstrated in many instances Roberts and Askey have reported that the periarterial injection of the temporal arteries with procaine hydrochloride (1–2 cc) produces definite and lasting relief of pain in those instances where the arteritis involves chiefly these vessels They report that in an instance where intracerebral arteries were involved, a stellate ganglion block was performed with satisfactory results This response suggests that the condition is vasospastic in nature No other form of therapy has been of consistent value Analgesics and sedatives usually do not afford complete relief from the pain The use of the opiates may be necessary, 'demerol and the newer opiate substitutes being preferred in the hope that they will not lead so readily to habituation

PERIARTERITIS NODOSA (ESSENTIAL PERIARTERITIS)

Until very recently there was no therapy which influenced favorably the course of this disease Symptomatic therapy was ordinarily unsatisfactory and did not prevent

position If such a bed is not available the patient should be placed in a bed with the head elevated at least six inches on wooden blocks *The limb should never be elevated above the level of the heart*

The foot and leg may be wrapped loosely in cotton batting but heat should never be applied locally Many limbs have been lost by injudicious use of heat

Reflex heat may be applied by the use of a heating pad on the abdomen or beneath the lumbosacral area Heat above 90° or refrigeration should never be applied directly to the involved extremity except when refrigeration is used as a pre amputation anesthesia Alcohol may be given in the form of whiskey or brandy, 1–2 oz every three to four hours depending upon the tolerance of the patient

Papaverine Hydrochloride

Papaverine hydrochloride, 0.6–0.1 Gm may be given intravenously or 0.3–0.6 Gm may be injected into the artery proximal to the occlusion Recent reports suggest that 0.2 Gm orally every four hours may be more effective than the smaller doses hitherto used

The injection of 60 mg of papaverine diluted in 5.0 cc of distilled water directly into the femoral or brachial arteries will frequently produce a striking increase in warmth and in some cases a conspicuous flush even in an extremity which was previously cold and cyanotic. This response has occurred in limbs which have failed to respond to repeated lumbar sympathetic blocks If the response is good the injection may be repeated every four to six hours the patient being observed carefully to avoid such untoward effects as excessive drowsiness and disorientation Morphine sulfate may be given intravenously in doses of 16 mg for pain and may be repeated by the usual routes of administration as necessary

Sympathetic Block

Paravertebral block often serves to increase the peripheral vasodilatation but it must be repeated several times within the first two or three days if the response is to be maintained The results of sympathectomy are unpredictable even if a preliminary paravertebral block causes a striking increase in circulation (as indicated by a rise in surface temperature and an improvement in the appearance of the limbs)

Paravertebral block should be avoided in patients receiving anticoagulant therapy because of the hazard of serious hemorrhage in the region of the puncture

An attempt may be made to produce a generalized sympathetic block with 'priscoline An intramuscular or intravenous injection of 25–75 mg of 'priscoline will adequately test the response of the patient with peripheral vascular disease The maximum therapeutic effects can be maintained by an oral dose of 25–50 mg every three to four hours Intravenous injection produces vasodilatation within two minutes intramuscular injection within ten minutes and oral administration within half an hour The reaction following oral administration is somewhat less intense than that following injection, but the duration of effect is somewhat longer Patients with coronary artery disease or with occlusive arterial disease elsewhere in the body, must be treated cautiously since a reduction in blood pressure may follow the administration of priscoline with serious consequences

The use of the pressure suction boot and intermittent venous occlusion apparatus has not, in our experience been found to meet the original claims

Anticoagulants

Anticoagulant therapy* is indicated in all instances of acute arterial occlusion to prevent propagation of existing thrombus

* See also Chapter 13

and of acute coronary occlusion following the self administration of ergot by mouth for the purpose of producing abortion or following the parenteral administration of ergot derivatives for therapeutic purposes Preparations containing ergot should not be administered over protracted periods of times unless *the patient is observed carefully* The drug should be withheld upon the slightest manifestation of toxicity, either local or general Once susceptibility to ergot has been demonstrated the drug should never be administered to the patient again

The treatment of vascular reactions to ergot consists of measures directed *to producing vasodilatation* The patient *should* be kept warm by means of warm blankets thermostatically controlled cradles, electric pads, or hot water bottles Whiskey or brandy should be given by mouth *every four to six hours* and papaverine hydrochloride injected intravenously in doses of 06–0 12 Gm every four hours Priscoline should be administered orally or parenterally at four- to six hour intervals until it is certain that all toxic effects of ergot have subsided completely

Syndromes Produced by Temperature Changes (Exclusive of Raynaud's Syndrome)

THERE are a group of diseases or syndromes (including most instances of Raynaud s phenomenon) which are the result of changes in the environmental temperature These syndromes have in common the abnormal reaction of blood vessels of the periphery of the body to changes in the temperature of the environment Usually an environmental temperature lower than that of the circulating blood is responsible for the reaction These conditions are produced by mechanisms with a certain similarity but their symptomatology is sufficiently different to warrant separation into different clinical groups

HYPERSENSITIVITY TO COLD MANIFESTED BY URTICARIA*

The treatment of hypersensitivity to cold is not satisfactory *Theoretically if the cold* sensitive patient is exposed to progressively cooler baths as—for example, by reduction of the temperature of the bath one degree each day—or if his hands are exposed to *progressively lower temperatures* histamine like substances released into his blood will produce an auto-desensitization However this has not been successful clinically

Desensitization may frequently be accomplished by the administration of *histamine* according to the following plan 0 1 cc of 1 1000 solution of histamine is injected intracutaneously Twice weekly the patient is given an intracutaneous injection increasing each dose by 0 1 cc. until 0 5 cc is reached The injections are then continued subcutaneously, the amount injected being increased by 0 1 cc until 1 0 cc is being injected Injections of 1 0 cc may be given twice a week thereafter

Patients frequently experience relatively severe reactions before this dose is reached *In these circumstances one must either* continue with the highest dose previously reached or reduce the dose to a point where a minimum reaction is produced

The results of this type of treatment are not spectacular Occasionally patients do

* See also Chapter 38

the consistently fatal outcome of periarteritis nodosa

Definitely beneficial results in the treatment of *early* cases of periarteritis nodosa have now been reported with the use of both *ACTH* and *cortisone* Some patients have remained in remission for substantial periods of time after four to six weeks of therapy About one half of all patients so treated require a minimum maintenance dose if relapse is to be avoided The dosage schedule of ACTH which appears satisfactory is 25 units a day for two weeks followed by a gradual reduction in dosage over the succeeding two to four weeks

Cortisone The suggested dosage of cortisone in the treatment of periarteritis nodosa is o 3 Gm the first day (o 1 Gm parenterally or four 25 mg tablets orally every 8 hours) o 2 Gm the second day (o 1 Gm parenterally or four 25 mg tablets orally every twelve hours) and o 1 Gm daily for two weeks (o 1 Gm parenterally each day or two 25 mg tablets twice a day) If the response to therapy is unsatisfactory after four to five days on this schedule the daily dosage may be increased to o 2 Gm or even o 3 Gm given in divided doses When maximum improvement has been attained the dosage should be reduced to the smallest daily maintenance dose that will prevent relapse The daily dosage should be increased to o 1–o 2 Gm if significant relapse occurs Intermittent courses of therapy with rest periods of four to six weeks have been useful in treating patients with rheumatoid arthritis and may be successfully applicable to patients with periarteritis nodosa

DISSEMINATED LUPUS ERYTHEMATOSUS INCLUDING LIBMAN-SACHS SYNDROME*

ACTH and cortisone have been found to produce at least a temporary beneficial effect in most *early* cases of disseminated lupus erythematosus Early diagnosis and prompt institution of therapy are essential

The favorable influence of these agents is manifested by a lowering of the patient's temperature by a reduction in the accelerated sedimentation rate, by amelioration of joint symptoms and, often by an improvement in skin lesions Usually the general condition of the patient is improved Evidence of renal involvement is ordinarily not altered and the so called L E cells in the bone marrow persist The beneficial effects of therapy tend to persist for periods of days to weeks but are not permanent as far as is known

Favorable responses do not usually occur —nor can they be expected—in advanced cases of lupus erythematosus especially in those with serious renal involvement as manifested by azotemia hypoproteinemia retinal hemorrhages and cachexia In cases of disseminated lupus erythematosus involving the heart and/or kidneys one must be watchful for evidence of salt and water retention and congestive heart failure during therapy with ACTH or cortisone

Strong sunlight is deleterious to patients suffering from discoid lupus erythematosus of the skin and mucous membranes and may produce a dissemination of the disease Such patients should reside in areas where there is the minimum of strong sunlight and they should avoid exposure to the direct rays of the sun Gold salts and bismuth compounds are used with some success in the local form of the disease but apparently are without any effect on the disseminated form The use of strong solution of iodide in doses o 15–1 o cc per day has been reported favorably in a few instances

ERGOTISM

Ergotism is largely a historical curiosity in the United States today but it is emphasized that drugs containing ergot should not be administered to any patient known to have a vascular disease There have been reports of attacks both of angina pectoris

* See also Chapter 38

the involved area This has been demonstrated repeatedly in experiments in animals and in man However, when frostbite is seen late anticoagulants are of doubtful value The reader is referred to the chapter on anticoagulant therapy for details of this treatment

Gangrene If gangrene is sufficient to require amputation the operation should *be delayed until a line of demarcation is* well established The region affected by gangrene in frostbite may be more superficial than appears at first Frequently blackened tissue peels off leaving a normal base of the deeper layers of skin or the subcutaneous tissues There should *not be any* haste to perform amputation every opportunity should be provided for the extremity to return as nearly as possible to normal before surgical interference is considered

TRENCHFOOT

This problem which is serious in war, is encountered rarely in civilian life It is a relatively simple matter in most instances to prevent trenchfoot Standing in water or mud soaked areas or remaining in cramped positions with prolonged immobility and dependency of the extremities should be avoided Well fitting waterproof, or water resistant boots with thick replaceable felt inner soles and wool socks should be worn Extra pairs of socks and of inner soles should be carried and wet socks and inner *soles should be exchanged for dry* ones as often as possible Shoes should be removed at least once a day and the feet cleaned and dried Individual hygiene is of the greatest importance The remainder of the body should be kept warm and dry The feet should be inspected frequently to insure proper hygiene

When trenchfoot has been diagnosed the patient should be moved without walking to the hospital In the early stages the greatest relief is obtained by elevating the legs and keeping the body warm and the feet cool Exposing the feet to the open air with a fan blowing over them continuously is often advisable until the hyperemic phase has subsided Ulcerated or gangrenous areas are treated by appropriate measures and pain is controlled by the administration of opiates and sedatives

In cases without gangrene, active and passive movement of the feet is begun as soon as *the hyperemia* has passed off It is extremely important that these patients become ambulatory at the earliest possible moment, but, because of the pain and annoying paresthesias which often accompany this condition, the patient may avoid *walking unless he is forced to do so* Exercises which do not require weight bearing are important in overcoming the patient's reluctance to exercise Such devices as stationary bicycles and swimming are useful Shoes must be well fitted and the patient made to walk early, with the aid of orthopedic devices If necessary, analgesics can be used to overcome the pain

Lumbar sympathetic block may be necessary to relieve coldness and paresthesias during this vasospastic stage and *lumbar sympathectomy* may be indicated if the response to sympathetic block is striking In patients with hyperhidrosis (excessive sweating) these measures ordinarily produce dramatic relief from this annoying symptom They have little or no effect on pain however

In cases with gangrene the gangrenous area should be protected from infection by the local use of suitable dressings and antiseptics or antibiotics The local circulation may be improved by injections of typhoid vaccine or other means of inducing fever The separation of devitalized tissue may be augmented by the use of conservative debridement and soaks in mild antiseptic solutions As the tissue demarcates it is carefully removed Amputation is delayed as long as possible since the amount of tissue which is eventually lost is ordinarily much

improve until they can be exposed to cold weather without developing urticaria In general, however, they continue to have local or generalized reactions on exposure to marked temperature changes

The antihistaminics may have a favorable effect on this syndrome although experience has not been sufficient to appraise this therapy Benadryl hydrochloride pyribenzamine hydrochloride or related compounds may prevent the development of cold urticaria if given in doses of 50–100 mg three times a day

FROSTBITE*

In civilian life frostbite can usually be prevented For those persons who are to be exposed to extreme cold clothing should be loose light warm and multilayered The outer layer should be of a windproof material In addition to wearing warm woolen socks and double layers of gloves one should have an extra supply of socks and gloves The best type of footwear is the Eskimo mukluk a boot which is made of seal skin with an inner layer of caribou skin Grass or a special moss or even paper may be stuffed in between these skins to improve the insulation If this type of footwear is worn and the feet are kept oiled and dry freezing is unusual If such footwear is not available large loose-fitting shoes should be worn over several pairs of woolen socks The feet should be washed daily and carefully dried and oiled preferably with an animal oil Skin lesions should be treated promptly Tight bands around *the leg must be avoided and the shoes* should not be laced tightly In brief nothing must be worn which impedes the normal circulation

Persons who are exposed to those conditions in which frostbite may occur must make every effort to keep moving since standing for even brief periods of time may result in frostbite Beards should not be grown by men who are exposed for long periods of time to unusually low temperatures since the moisture from the expired air freezes on the hairs of the beard and increases the risk of frostbite of the face

Frostbite is a vascular emergency and prompt application of proper treatment increases the chances for saving the extremity In general the object in treating frostbite is similar to that in treating acute arterial occlusion to relieve the ischemia of the tissues

For mild or first degree frostbite, the hand or limbs should be placed in a warm environment until the circulation is restored to normal Heat greater than that of a normal room warmth should be avoided In more severe cases it is important that the wrong things should not be done The skin should not be rubbed energetically or traumatized in any way since the vascular insufficiency predisposes the tissues to damage *Snow should not be applied* After the feet have been frozen the patient should not continue walking if this can be avoided If the patient can be removed to a dwelling or to a hospital the extremities should be warmed slowly by exposure to heat no greater than that of the natural room temperature Warm drinks or alcoholic beverages frequently the only vasodilators available should be given liberally but not in excess It may be wise to paint the exposed area with a mild antiseptic such as 1 1000 acriflavine or 1 5000 'merthiolate'

The speed with which the feet or limbs are warmed should not be too rapid because of the excruciating pain which may occur This is usually avoided if the feet are exposed to not more than room temperature If however the patient complains of pain the limb may be cooled slightly It is apparently well established that the early administration of heparin to patients suffering from frostbite reduces the incidence and degree of gangrene by preventing thrombosis in the blood vessels supplying

* See also Chapter 25

Lumbar sympathetic block and lumbar sympathectomy may be indicated in severe cases

LIVEDO RETICULARIS

Livedo reticularis is of concern to the majority of patients only because of its cosmetic effects. The etiology of the condition is not known and there is no specific therapy for it The symptoms in the average instance are mild and it may persist for years without evidence of progression

The most important factors in the management are the protection of the body as a whole, and of the involved parts in particular from exposure to cold In the rare instance in which gangrene or ulceration occurs, bed rest and the use of all measures favorable to vasodilatation are indicated When severe livedo reticularis involving the lower extremities has progressed to gangrene and ulceration lumbar sympathetic block or lumbar sympathectomy may be tried but the results have been disappointing if followed for a few months or years

Organic (Structural) Conditions: The Nonocclusive Arterial Diseases

ANEURYSM

There is no medical treatment for aneurysm per se Surgical technics have been developed for aneurysms of various types and in various locations in the body Aneurysms of the peripheral vessels especially those in the popliteal space may be obliterated or removed surgically with considerable success The reader is referred to surgical text books for a discussion of this therapy

ARTERIOVENOUS FISTULA

When arteriovenous fistulas are single or few in number they may be closed successfully by surgical means In many instances, however, the communications are numerous Ligation of the artery proximal to the site of such multiple communications or simultaneous ligation of the artery and its accompanying vein are ordinarily of little value When a single digit is involved, as is occasionally the case, amputation may be advisable

Treatment with radium is indicated only in those instances when the radium can be applied directly to superficial angiomatous areas Injection of the superficial veins with sclerosing solutions is only rarely successful When the fistulas are in the lower extremity and superficial the palliative measure of compressing the abnormal connections by the wearing of an elastic or pure rubber bandage or stocking may be satisfactory

The problem of arteriovenous fistula is primarily surgical and the reader is referred to the definitive monograph by Emile Holman for a full discussion of the subject *

* *Arteriovenous Aneurysm* New York Macmillan 1938

less than anticipated Skin grafting over areas which have been severely involved is often necessary

IMMERSION FOOT

Prophylaxis against immersion foot includes the following measures Warm waterproof clothing and covering is desirable the boots should be waterproof and loose fitting and every effort should be made to keep the feet as dry as possible several pairs of socks should be available so that when socks become wet they can be removed the feet should be dried and covered with a thin layer of oil petroleum jelly or a heavy grease and the boots and socks should be well dried before being used again It is important to avoid cramped positions and prolonged dependence of the extremities and this can be done by exercising and elevating the feet temporarily at frequent intervals

The upper part of the body should be kept dry and exposed as little as possible to cold winds Any constriction about the arms or legs by tight clothing shoes socks or garters should be avoided Nutrition should be maintained at a high level Alcohol should be avoided

When the feet are severely involved the patient should not be permitted to walk. He should be placed in a warm environment but not in one heated excessively The feet should be elevated and kept moderately cool if necessary by ice bags or a spray of water or by directing a fan over them Involved skin should be painted with a mild antiseptic and wet dressings or penicillin may be applied if infection is present Heat and strong antiseptics should never be applied to the skin of the affected area

As soon as the swelling has subsided and does not recur on dependency and when all ulcerations are healed the patient should be encouraged to become ambulatory Pains and paresthesias, similar to those of trenchfoot occur following immersion foot and may cripple the patient Physiotherapy is invaluable in rehabilitating these patients * Persons who have suffered a severe attack of immersion foot should seek indoor employment thereafter since discomfort and even distress may occur upon further exposure to cold

ACUTE PERNIO (ACUTE CHILBLAINS)†

Because of the local ischemia produced by the severe vasospasm of this condition protection of the local area against trauma and infection is important The application of collodion film to small areas will serve to protect against minor trauma such as produced by scratching Broken blebs and ulcers should be treated with a mild antiseptic or covered with an ointment containing a suitable antibiotic and dressed aseptically Excessive heat (above 85° F) should be avoided or burns may occur The lesions should not be rubbed vigorously with snow since this will serve only to traumatize further the skin and underlying tissues

CHRONIC PERNIO (CHRONIC CHILBLAINS)

There is no specific treatment for chronic pernio The patient should be protected from exposure to cold and dampness and it may be desirable for him to live in a warm climate if he can possibly do so In mild cases and where the patient is able to avoid exposure to intense cold the prognosis is good The use of "mecholyl iontophoresis three times a week has been of some value when patients have carefully protected their legs from further exposure to intense cold Artificial fever therapy produced by the intravenous administration of typhoid vaccine may give symptomatic relief and hasten the healing of ulcers

* See also Chapter 45
† See also Chapter 28

therapy reduces the risk of venous thrombosis.

Patients bedridden following *major surgery*, particularly of the abdomen and pelvis, or instrumental and complicated *deliveries and those who are seriously ill* or debilitated are prone to develop venous thrombosis and pulmonary embolism. Preventive *measures in all* instances should include frequent deep breathing exercises, passive and active exercise of the feet and legs, massage of the legs, adequate hydration, adequate treatment of any infection, early ambulation, maintenance of optimum environmental temperature and, where the risk of venous thrombosis is considerable, *anticoagulant therapy*.

Additional prophylactic measures in surgical, obstetrical, and accident cases include meticulous surgical technic which avoids trauma to the tissues and blood vessels as far as is possible, avoidance of pressure on the legs during and after operation and avoidance of excessive abdominal and inguinal compression from tight bandages, dressings, and adhesives.

There has recently been an increase in the *frequency of venous thrombosis* resulting from *prolonged dependency and immobilization* of the legs in persons who travel long distances by airplane, railroad coach, bus or automobile. The venous stasis in such instances is aggravated in women by girdles which compress the venous channels when the wearer is seated. Prophylaxis consists simply of exercising periodically by walking about the plane or train at intervals no greater than every two hours, or by dismounting from the bus or automobile at every stop and walking until the trip is resumed. Women should avoid *the wearing of constricting* garments such as girdles or circular garters, when making such trips.

Active Treatment

It is important to examine the legs of bedridden patients daily to observe at the earliest possible moment the development of *thrombophlebitis* or phlebothrombosis. Active *treatment of incipient venous thrombosis* at the onset is important, particularly since phlebothrombosis, which *may present the most innocuous local effects* is most apt to be the source of a pulmonary embolus.

Localized thrombophlebitis of the *superficial veins* usually responds to elevation of the leg and the application of hot, moist packs. Thrombophlebitis of *the long or short saphenous veins*, the *deep veins of the calf*, or of *sizeable varices* will respond ordinarily to the same measures, but the packs must be extended for the full length of the *leg and treatment must be continued until* all tenderness has disappeared, usually a period of from seven to ten days.

When thrombophlebitis involves the *femoral vein* or the *iliofemoral junction* the leg should be *elevated and packs applied* from the ankle to the groin as follows. The skin is first anointed with a thin layer of lanolin, petroleum jelly, or baby oil and is then covered with a single layer of surgical gauze. Pieces of flannel of double *thickness or turkish towels of sufficient size* to cover the entire limb are dipped in boiling water, wrung as dry as possible and *applied to the limb*, the attendant *being* careful not to burn the skin. A rubber cloth is fastened around the flannel and a heavy bathtowel around the rubber. *Hot* water bottles may be placed outside of the bathtowel. Moist heat is more effective than dry heat and is less apt to burn the patient.

Pain may be sufficiently severe for a few days to require the use of sedatives or even opiates but within three or four days the patient usually will be able to move his leg comfortably. He is then encouraged to exercise his toes and feet and to shift his position frequently. More vigorous movement *of the affected limb* may provoke considerable local distress as long as the inflammatory reaction exists. When pain, tenderness and *swelling have* subsided and the pa

12. Vascular Diseases

II. Diseases of Veins, Lymphatics, and Capillaries

CHARLES D. MARPLE
& IRVING S WRIGHT

Organic (Structural) Conditions (Obstructive)

THROMBOPHLEBITIS AND PHLEBOTHROMBOSIS (VENOUS THROMBOSIS)

Prophylaxis

One or several factors may predispose a patient to an attack of thrombophlebitis or of phlebothrombosis Prevention depends upon the successful management of predisposing disease the avoidance of precipitating trauma the prevention of venous stasis and the maintenance of normal hemostasis The patient who has had one attack of thrombophlebitis or phlebothrombosis is apt to have a subsequent attack frequently because of a predisposing disease usually because the resulting venous insufficiency predisposes to further attacks

Thrombophlebitis secondary to *thromboangiitis obliterans* is less apt to occur if the progress of the thromboangiitis is halted The avoidance of tobacco will decrease the risk of thrombophlebitis Measures improving the blood flow whether by vasodilatation or mechanical means will lessen the likelihood of thrombosis The use of anticoagulant therapy will reduce the risk of venous thrombosis and of sudden arterial occlusion

Thrombophlebitis is less apt to complicate a *blood dyscrasia* if the primary disease can be controlled Anemia and debilitation must be avoided as far as possible Transfusions must be given cautiously since they may be followed by severe and extensive thrombosis Hypercoagulability of the blood may necessitate the use of anticoagulants but these must be administered cautiously in the presence of a blood dyscrasia because of the risk of hemorrhage

The control of thrombophlebitis secondary to an *infectious disease* usually depends on the adequate treatment of the primary disease by chemotherapeutic methods In the presence of *heart disease* venous stasis and hypercoagulability of the blood are favored by congestive heart failure and by cardiac arrhythmias Anticoagulant

emergencies and require immediate and energetic treatment *The patient is placed in an oxygen tent and given 50 mg of heparin, 30 mg of papaverine, and 0 6 mg of atropine sulfate intravenously immediately* Heparin is continued according to *the plan outlined in Chapter 13 Dicumarol* may be administered orally from the first day and heparin may be discontinued when the prothrombin time is prolonged sufficiently The patient is kept warm, pain is *controlled* by codeine or morphine, and papaverine is given regularly every four hours until the acute phase has subsided

The patient should be kept in bed until all signs and symptoms have subsided, ordinarily a matter of a week or more, but anticoagulant therapy is continued for an additional two to three weeks Shock* must be treated by all appropriate means, including blood transfusion which must be given cautiously and preferably after the institution of anticoagulant therapy If transfusion is given during heparin therapy, an additional dose of 50 mg of heparin should be given immediately after the transfusion

Management of the Postthrombophlebitic Patient

The patient with thrombophlebitis may recover rapidly and uneventfully from the acute inflammatory process and yet develop *chronic venous insufficiency* unless managed properly during the early period of ambulation A venous circulation which is adequate when the patient is confined to bed may be inadequate when the hydrostatic venous pressure in the erect position adds insult to the venous system already damaged by inflammatory reaction, partial obstruction, secondary dilatation, and incompetent valves

Elastic Stockings In all instances of moderate or severe thrombophlebitis of the lower extremity, the patient should not be allowed out of bed until he has been fitted with a *knee length elastic stocking* which he wears at all times when ambulatory We do not use full length stockings since venous insufficiency is manifested almost wholly in the lower leg and because it is almost impossible to apply a comfortable and efficient elastic support above the level of the knee

An elastic stocking must be fitted to the leg when the latter is free of edema This stocking is applied before the patient leaves the bed in the morning and is worn during the entire day, except that it may be removed during such times as the patient is able to rest in bed with the foot elevated For the sake of comfort, the stocking may be removed on one or two occasions during the day, but reapplied shortly After a period of three months the elastic support may be discarded for half a day to determine if edema appears If it does the stocking is worn for another month If edema does not appear within one half day without support the patient may try a full day without support The support may be discarded only when edema does not appear in its absence Usually it must be worn for *at least three months, often for six months* and occasionally for a year The alternative is chronic venous insufficiency with all of its complications

During the first four to eight weeks following ambulation *the patient should sleep at night with the foot of the bed* elevated eight to ten inches Later he should exercise his leg regularly with bicycle exercises in bed and by swimming

Prolonged rest in bed *following* thrombophlebitis is not desirable because of the danger of muscular atrophy and osteoporosis When the acute process has subsided these are minimized or prevented by massage, by exercise of the legs while the patient is in bed, and by early ambulation The leg must be supported properly for

* See also Chapter 43

tient's temperature has been normal for several days the treatment may be discontinued and the patient allowed out of bed This will require ordinarily ten to fourteen days

In instances of *axillary* and *subclavian* thrombophlebitis the treatment is identical except that the patient need not be kept bedridden after the first five days if proper elevation can be maintained while he is sitting in a chair

Ligation Ligation of the femoral vein in femoral thrombophlebitis of the iliac vessels or inferior vena cava in iliofemoral thrombophlebitis and of the long saphenous vein in thrombophlebitis involving that system is not desirable ordinarily It is not rational for the prevention of pulmonary embolism because acute thrombophlebitis is somewhat less apt to produce emboli than is phlebothrombosis and because anticoagulant therapy will better secure this objective Many fatal pulmonary emboli arise from sites not recognized during life and hence from veins which would not be those selected for ligation Furthermore we have seen several deaths caused by emboli arising from sites proximal to those at which ligation has been performed When anticoagulant therapy is carried out properly it is definitely the treatment of choice Even if ligation is performed anticoagulants should be administered following ligation Ligation of the iliac veins or of the inferior vena cava is indicated when thrombophlebitis ascends rapidly in the thigh and promises to progress further despite energetic conservative therapy Venous ligation is indicated also when multiple pulmonary emboli arise from a phlebitis of the leg and properly controlled anticoagulant therapy is not available

Sympathetic Block Lumbar sympathetic block may be performed in those instances in which thrombophlebitis is accompanied by a high degree of vasospasm in the affected limb but this should not often be necessary since a moderate degree of vasospasm will respond usually to elevation, heat, and appropriate sedation or analgesia In instances of severe vasospasm sympathetic blocks should be performed at intervals of eight to twelve hours during the first twenty four to forty-eight hours

Prevention of Pulmonary Embolism

Pulmonary embolism is more apt to occur secondarily to a phlebothrombosis of the deep veins of the plantar region, of the calf, or of the thigh than it is secondarily to an inflammatory thrombophlebitis It is for this reason that the routine daily examination of the leg for evidence of venous thrombosis is advised for all bedridden patients Fatal pulmonary emboli may occur from inflammatory thrombophlebitis at any time and it is beyond the ability of any physician to know when embolization is imminent All patients with phlebothrombosis or with thrombophlebitis are candidates for intensive anticoagulant therapy * Prophylactic treatment, irrespective of whether a pulmonary embolus has or has not already occurred is immediate institution of anticoagulant therapy In instances where a warning pulmonary embolus has already occurred heparin and 'dicumarol' should be administered immediately and the heparin continued until the prothrombin time has been sufficiently prolonged to assure protection to the patient. In instances of phlebothrombosis where pulmonary embolism has not occurred, it usually is sufficient to give dicumarol alone

Treatment of *small pulmonary emboli* includes anticoagulant therapy, the administration of opiates and analgesics to control pleural pain and rest in bed until all symptoms and signs of embolism have disappeared usually about one week Anticoagulants should be continued for three to four weeks after the embolic episode

Treatment of Large Emboli Large emboli particularly those producing acute cor pulmonale and shock, are serious vascular

* See also Chapter 13

tation due to age or constitutional disease, and usually pregnancy In multiparous women who have suffered from their varicosities during earlier pregnancies injection and even ligation may be done during the second trimester Sclerosing solutions containing quinine must be avoided

Technic of Injection While a variety of solutions may be used as sclerosing agents for varicose veins 5 per cent solution of sodium morrhuate is satisfactory A series of injection treatments should be preceded always by the preliminary injection of a test dose of 0 5–1 0 cc intravenously to determine if the patient is hypersensitive to the solution Such sensitivity may be manifested by local or generalized erythema and pruritus which may appear in from a few minutes to twenty four hours and is more apt to occur in patients who are allergic to other substances Should sensitivity be manifested, another sclerosing agent such as 3 5 per cent sodium ricinoleate should be tried

The injection of varicose veins should be done, when possible with the patient in the erect position preferably standing on a platform or treatment table Injections are given at intervals of one to several days and no more than 2–4 cc of sclerosing solution is injected at any one time The first injection is given at the proximal or upper end of the varicosed vessel and subsequent injections are given distal to this point The physician must be certain that the sclerosing solution is injected into the vein and not into its wall or into the perivascular tissues because extravasation will be followed by painful serious local reactions The site of injection is covered with a sterile gauze square and the injected vessel is compressed by the application of an elastic bandage or stocking

Vasovagal attacks following the injection of sclerosing solutions in sensitive and anxious patients may be prevented by giving such patients a small dose of one of the barbiturates half an hour prior to injection and by having the patient lie down immediately following injection An attack may be aborted by having the patient sniff aromatic spirits of ammonia *Generalized erythema* with or without urticaria is treated by injecting 0 5–1 0 cc. of 1 1000 epinephrine hydrochloride and 40 mg atropine sulphate hypodermically

For the rare case of postinjection collapse with shock epinephrine atropine, and papaverine should be given intravenously and oxygen and carbon dioxide administered by mask Local reactions due to the escape of the sclerosing solution from the vein should be treated by the injection of 1 0–2 0 cc of isotonic solution of sodium chloride locally to dilute the sclerosing agent, rest, and appropriate sedation or analgesia

CHRONIC VENOUS INSUFFICIENCY

In patients with chronic venous insufficiency all extensively varicosed superficial veins should be ligated or injected or both provided that the deep veins are competent The patient's bed should be elevated at least 6 inches *at the foot* so that the veins and tissue spaces will tend to drain well during the night Preliminary to the use of an elastic support to the leg the patient should be put to bed with the leg elevated until all edema has disappeared

An elastic stocking fitted to the patient or an elastic bandage is then applied before the patient leaves his bed and is worn at all times when he is ambulatory This elastic support extends from the base of the toes to the knee but not above the knee Even while wearing an elastic support the patient should avoid walking for long distances or standing for long periods of time

*Dermophytosis** is treated by soaking the feet in a warm solution of 1 5000 to

* See also Chapter 38

weight bearing Prolonged bed rest is undesirable also because of the risk of postphlebitic neurosis, a not uncommon sequel in the apprehensive and anxious patient. Postphlebitic neuritis is another uncommon complication which may be managed ordinarily by a single or repeated block of the involved nerve with procaine Active motion of the leg including ambulation and an encouraging and reassuring attitude on the part of the physician are important in overcoming these complications

Organic (Structural) Conditions (Nonobstructive)

VARICOSE VEINS

The prophylactic or conservative management of varicose veins while unsatisfactory may be used for patients with early or mild varicosities or for those for whom more active treatment is contraindicated. The measures employed in combination include adequate periods of rest with the feet and legs elevated avoidance of standing, avoidance of constrictions about the legs and hips such as those produced by the wearing of tight garters or tight girdles, and support of the legs by elastic bandages or stockings The pelvis and the abdomen should be examined to determine if there is any obstruction to the venous return from the legs This type of management should be applied to the degree indicated in the individual patient in every instance of pregnancy

Active Treatment

Active treatment of varicose veins consists of the injection of sclerosing solutions and the ligation or extirpation of varicose veins surgically These two procedures may be done individually or together in a given case

Sclerosing Solutions The treatment of varicose veins by injection of a sclerosing solution alone produces satisfactory results consistently only when applied to small superficial varices of a telangiectatic nature (commonly referred to as "spider burst varices) or to mild localized varicosities that are not associated with any demonstrable incompetency of the greater or lesser saphenous systems

Surgery Mild moderate, or severe varicosities associated with incompetency of the great or small saphenous veins must be treated by surgery if permanent improvement is sought This consists, usually, of dividing the greater saphenous vein at the saphenofemoral junction In patients with severely varicosed veins in the short saphenous system this vein may be ligated and divided in the popliteal space

Subsequent to operation small and localized areas of residual varicosity may be obliterated by injection It may be necessary to ligate several of the veins communicating between the superficial and deep venous systems to assure a satisfactory result Excision and stripping of veins has gained popularity since the results by this technic seem to be more permanent than those obtained by other methods

Contraindications to Injection Treatment by injection of sclerosing substances is *contraindicated* in the presence of serious heart disease with congestive heart failure and advanced coronary sclerosis uncontrolled diabetes mellitus blood dyscrasias severe thyrotoxicosis acute infectious disease occlusive arterial disease in the affected extremity active cellulitis, lymphangitis or infection in the affected leg recent acute thrombophlebitis, extreme obesity, intra abdominal malignancy, debili

slightly larger in area than the ulcer itself. This is held in place by means of a strip of "elastoplast" adhesive bandage. Support to the leg is provided by the application of *an elastic bandage, a well fitted elastic stocking* or an Unna's paste boot. The elastic supports have the advantage that they can *be removed each day and the ulcer cleaned* and dressed. The paste boot has the advantage that the patient cannot tamper with it. The *important factor in the ambulatory* treatment of stasis ulcers is the prevention of edema. If after a fair trial healing or improvement is not satisfactory, there is no alternative but to place the patient at rest in bed.

Following the healing of a stasis ulcer, the elastic support to the leg must be worn *for a long period of time* often for a year or two, in fact not uncommonly for the rest of the patient's life. Where the area of ulceration is one on which even an elastic support will not exert pressure as, *for example*, around the perimeter of the malleoli, a rubber sponge or molded latex pad *should be worn beneath the elastic support. Ulceration is* apt to recur if venous insufficiency is not permanently controlled and local trauma avoided.

All ulcers of the lower leg are not the result of venous insufficiency. They are for example not uncommon complications of *sickle cell anemia and of pernio. In some* instances of hypertensive cardiovascular disease, ulcers of the skin develop secondary *to ischemic infarction which in turn is* produced by sclerosis and occlusion of small cutaneous arterioles. These ulcers *heal slowly even when the patient is placed* at rest in bed. The application of lyocyte powder appears to promote their healing.

Diseases of the Peripheral Lymph Vessels

LYMPHEDEMA

If medical treatment of lymphedema is to be completely effective it must be instituted *shortly after* the lymphedema has first appeared. The longer lymphedema exists the more fibrosis occurs. Long standing lymphedema is associated with advanced fibrosis which will not respond to *any measure short of surgical extirpation*. In a sense early lymphedema may be looked upon as a condition similar to the *edema secondary to* varicose veins. In lymphedema the lymph vessels are dilated, their veins incompetent and the lymph is static. Increasing back pressure leads to effusion into the tissue spaces. The objects of *medical treatment are to support* the lymph vessels to prevent stasis and to assist in moving the lymph toward the trunk. This is accomplished by compressing the limb with adequate elastic support.

Before a compression bandage or stocking is fitted to the patient's leg the edema must be removed from the leg as far as possible by placing the patient in bed with the foot and leg elevated. It may be advisable to suspend *the affected leg in a sling* to increase the degree of elevation.

Nonelastic cloth bandages are of no value. We *prefer elastic stockings* to elastic bandages because elastic bandages are difficult to apply, they tend to slip and curl and it is almost impossible to wrap them so that they exert pressure evenly over the entire leg. *On the other hand* elastic stockings require expert fitting, they lose their elasticity after repeated washing and they are expensive. The single criterion by which to judge the effectiveness of the device is whether or *not it prevents* edema formation.

An elastic or pure rubber bandage can

1 10 000 potassium permanganate for thirty minutes once or twice a day More potent fungicides may be used if necessary but are undesirable because of the risk of producing a chemical irritation of the devitalized and denuded tissues A mildly fungicidal dusting powder such as desenex can be used when the fungus infection is controlled

*Eczematoid skin reactions** will improve as the venous stasis is corrected Symptomatic measures are necessary to relieve the pruritus If because of pain itching and oozing of the lesion an elastic support cannot be worn the patient should be kept in bed Subjective relief may be obtained by the application of 3 per cent ichthammol (ichthyol) in zinc oxide ointment or by dressings moistened with 0 5 per cent aluminum subacetate solution or 0 01 per cent potassium permanganate Ten per cent ethyl aminobenzoate ointment (benzocaine or anesthesin) has been a satisfactory antipruritic in our hands

When there is *chronic cellulitis* it is necessary to place the patient in bed for several weeks and to apply warm wet dressings to the elevated extremity Such cellulitis is accompanied frequently by an advanced degree of chronic induration which responds slowly to treatment

Pigmentation of the skin in areas of chronic edema and venous congestion often masks the presence of petechial hemorrhages which are increased in numbers by prolonged walking or standing These tiny hemorrhages are produced by rupture of the minute vessels resulting from increased back pressure and local nutritional deficiencies In many patients the determination of capillary fragility and of the vitamin C level in the blood will demonstrate subclinical scurvy The addition of 0 3 Gm of vitamin C to the diet each day will prevent these hemorrhages and may accelerate the healing of ulcers if these are present It is probably advisable to administer 20–60 mg of rutin to these patients even though the role of rutin in preventing these capillary hemorrhages is not proved

* See also Chapter 38

Stasis Ulcer

The patient with a stasis ulcer should be placed in bed with the extremity elevated until the edema has been reduced If clean the ulcer or ulcers are exposed to the air to dry if infected they are covered with wet dressings of 100 to 1000 units of penicillin per cc of physiologic saline or 0 05 per cent suspension of tyrothricin in distilled water If there are varicose veins draining the area of ulceration these should be treated by ligation since healing of the ulcer may never occur or the ulcer may continue to recur unless the retrograde blood flow in the varicosed veins is prevented The skin surrounding the ulcer should be protected by the application of a bland and soothing ointment Healing of clean ulcers may at times be accelerated by the application once a day of dried human erythrocytes (lyocyte powder) The use of compression by binding rubber sponges over the areas of ulceration by the application of elastoplast bandages or of Unna s paste boot is frequently of value when edema has subsided The application of a split thickness skin graft to ulcers of large size will speed the period of recovery but cannot be done until the ulcer is clean and healthy in appearance

Many patients with venous insufficiency complicated by stasis ulceration will be unable to remain in bed for the period of time necessary for the ulcer to heal If the ulcer is not too extensive and if it is not grossly infected it may heal while the patient remains ambulatory The patient should be kept in bed until existing edema has subsided The ulcer is cleansed and covered with a sterile gauze Pressure is exerted to the ulcerated area by a piece of sponge rubber about a centimeter in thickness and

Tumors of Blood Vessels

TELANGIECTASIA

Spider Nevi

Spider nevi may be removed for cosmetic reasons by applying an electrocautery needle to the central vein They may also be removed by injecting a minute amount (0 1–0 3 cc) of sodium morrhuate into the central vein with a 26 gauge needle Senile ectasia (senile vascular nevi) may be removed for cosmetic reasons by fulguration

Hereditary Hemorrhagic Telangiectasia (Rendu Osler Weber Syndrome)

The lesions of hereditary hemorrhagic telangiectasia are of more than cosmetic interest because of their marked tendency to bleed Frequent epistaxis from nasal lesions is the most common symptom but lesions on the mucous membrane of the mouth lips or pharynx and on the fingers are also prone to bleed readily This bleeding tends to be profuse and to occur with sufficient frequency to produce a significant hypochromic anemia Blood transfusions may be necessary to combat the severe anemia which develops It has been reported that the administration of rutin in doses of 20–60 mg three times a day orally effectively decreases the frequency and severity of bleeding in that condition

The destruction of local lesions may be carried out by the application of radium by cautery or by such caustics as chromic acid Electrocoagulation with a current of high voltage and of low amperage may be done under local anesthesia or under sodium pentothal narcosis

HEMANGIOMA

The treatment of most hemangiomas is difficult and the outlook for complete cure is ordinarily poor The treatment of hemangiomas of the face and neck should be done by an experienced plastic surgeon

Nevus Flammeus (Port wine Nevus Birthmark)

Removal of port wine nevi for cosmetic purposes may be accomplished by the application of radium, excision followed by skin grafting or by the application of 25–50 per cent chromic acid Most forms of treatment are apt to leave scars which are more disfiguring than the original lesion For this reason, treatment should be undertaken only by a physician experienced in the management of such problems Port wine nevi on women can be covered satisfactorily in many instances by the appropriate use of cosmetics

Capillary Hemangioma (Strawberry Nevus)

These lesions may be destroyed by freezing for five to ten seconds by the application of a stick of carbon dioxide snow under light pressure They may also be treated by the application of radon seeds of roentgen rays, or by surgical excision

Cavernous Hemangioma (Cavernous Nevus)

The implantation of radon seeds or electrocoagulation are the methods of choice in treating cavernous hemangiomas about the face and neck The injection of a sclerosing solution such as 5 per cent sodium morrhuate may be used Ordinarily small amounts (0 5–3 0 cc) of the solution are injected at one time and compression applied immediately for a period of five to ten minutes Several injections are ordinarily necessary and are given usually at intervals of a fortnight High voltage roentgen therapy has been the most successful therapy for deep seated hemangiomas such as those involving the bones and the viscera Surgical excision may be used if the size and location of the lesion permit

be obtained in various widths, lengths, and weights The heavier weight should be used for the more intractable edema The bandage is applied over a lisle stocking beginning with two turns about the foot, two figure-of-eight turns about the ankle and continuing up to the knee The ideal tension on the bandage must be learned by experience If the bandage is too tight, the toes become cold and numb if too loose, edema appears

The bandage or stocking should be applied in the morning before the patient steps out of bed and should be worn without exception during the time the patient is ambulant If possible the patient should rest the leg elevated for an hour each midday the stocking or bandage may be removed during this time He should possess several bandages and at least one extra stocking so that he need not be without support when one is being washed The wearing of a lisle stocking under the elastic support will prolong the interval between washing and prolong the life of the support Some patients complain of the cosmetic appearance of the bandaged leg It may be pointed out to them that the edema also is disfiguring

The length of time during which the support must be worn cannot be estimated in advance In long standing cases in which there is severe damage to the lymphatics and advanced fibrosis it may be necessary for the patient to wear an elastic support permanently In early cases it may be possible to remove the support after a period of three to six months The support should be worn again if edema reappears In fact, it should be worn whenever the patient stands or walks for long periods of time

Surgical treatment does not offer sufficient promise of success to warrant its application to the mild cases of lymphedema especially in young women It does however, fulfill an important need in advanced and extensive elephantiasis The most popular procedure is the Kondoleon operation or a modification thereof A technic has recently been described which involves the insertion of threads beneath the skin to encourage the drainage of lymph around sites of obstruction

The treatment of lymphedema of the arm, a frequent sequel to radical resection of the breast, is based upon similar principles to those outlined for the legs Dr William T Foley of New York City has designed an elastic half glove and sleeve which has been helpful in the care of these patients

LYMPHANGITIS

Acute lymphangitis is always a serious condition It is especially so when it involves limbs rendered relatively ischemic by obliterative vascular disease Lymphangitis is treated by placing the patient in bed, elevating the affected limb, applying hot moist packs and administering sulfonamides or antibiotics

The *hot packs* should be applied from the toes to the groin when the leg is involved and from the fingers to the axilla when the arm is involved A search must be made for the primary site of infection, for which the portal of entry may be a superficial abrasion, a fissure between the digits, or a chronic leg ulcer

Local treatment must include the elimination of factors predisposing to the infection, the eradication of epidermophytosis which is undermining and destroying the interdigital epithelium, the removal of eschar which is preventing the drainage of infected wounds or ulcers and the incision and drainage of local abscesses Recurrent lymphangitis complicating a peripheral vascular disease will not be prevented unless the predisposing conditions arising from the presence of the primary disease are eliminated

of vitamin C deficiency, but, *in the absence* of evidence for another cause, it is an indication for determining the plasma vitamin C level, or for administering vitamin C as a therapeutic test

The response of the patient depleted of vitamin C to the therapeutic administration of the vitamin is prompt and dramatic. Symptoms arising from vitamin C deficiency should disappear completely in from three to seven days on a regimen which includes 0 25 Gm of ascorbic acid, or 16 ounces of fresh orange juice each day Parenteral administration of ascorbic acid is ordinarily unnecessary as the vitamin is absorbed readily in the absence of intrinsic disease of the gastrointestinal tract

Occasionally elderly patients are unable to utilize vitamin C when it is administered orally and must be given ascorbic acid parenterally once a week to maintain good health The lack of a prompt response should be taken as evidence that the increased capillary fragility is not due to vitamin C deficiency

Extracts of paprika and of lemon peel (citrin) restore to normal the increased fragility of capillaries in certain instances not associated with vitamin C deficiency The active principle, designated as *vitamin P*, has not been identified chemically Vitamin P activity has been demonstrated in extracts from a variety of natural foods including oranges lemons, grapes, and other fruits and vegetables The therapeutic effect ascribed to vitamin P is provided by the administration of hesperidin methyl chalcone orally in doses of 50–100 mg one to four times a day It has been claimed that rutin, a flavone glucoside closely related to hesperidin chemically, diminishes the increased capillary fragility in certain instances when administered orally in doses of 20–60 mg three to four times a day

INFECTIOUS PURPURAS

Purpura occurs in association with many types of infection The increased capillary fragility may or may not be accompanied by thrombocytopenia In septicemias due to a variety of bacterial agents, the petechiae are caused by minute emboli When emboli are not present, the phenomenon is presumably due to an increased capillary fragility resulting from the action of toxins on the capillary endothelium The treatment is directed primarily to the underlying infectious disease

TOXIC PURPURAS

Purpura, with or without thrombocytopenia, may follow the administration of a variety of drugs In some instances, the reaction appears to be in the nature of an allergic response, but in others it is due to a direct toxic effect of the drug on the capillary endothelium In addition to the heavy metals the barbiturates, benzol, dinitrophenol, quinine, ergot iodides, belladonna and the sulfonamides have been implicated Management consists of immediate withdrawal of the drug the application of measures designed to hasten its excretion, and specific treatment of its toxic effects *

HEMATOGENIC PURPURAS

Purpura is not infrequently associated with various diseases of the blood, for example, with the leukemias, especially the acute forms aplastic anemia, the myelophthisic anemias due to multiple myeloma myelosclerosis or to metastases to the bone marrow, advanced pernicious anemia, Banti's disease, Gaucher's disease, Felty's syndrome, and following irradiation † Often there is thrombocytopenia

Treatment of primary or idiopathic

* See also Chapter 50
† See also Chapter 14

Diffuse Hemangioma

These lesions are usually not amenable to any measures other than the injection of sclerosing solutions and this is apt to be unsuccessful because of the number and extent of the sinuses When diffuse hemangiomas occur on the lower limbs, venous ligation and retrograde injection of sclerosing agent may be performed and an elastic stocking worn thereafter

Racemose Hemangioma (Cirsoid Aneurysm, Congenital Arteriovenous Fistula)

These hemangomas are essentially arteriovenous fistulas and are treated as such

MALIGNANT TUMORS OF THE BLOOD VESSELS

Hemangioendotheliomas and Hemangiosarcomas

The differentiation of the various types of malignant lesions arising from the blood vessels is beyond the scope of this volume The treatment of all such lesions is wide excision if this is possible and if metastasis has not occurred Many of these tumors are sensitive to roentgen radiation, but in many instances this proves to be only a palliative measure When the lesion arises in a limb amputation may be the only means of securing a cure

Kaposi s Sarcoma (Multiple Idiopathic Hemorrhagic or Pigment Sarcoma)

Careful and repeated roentgen treatment of the lesions of Kaposi s sarcoma may often delay the progress of the disease and prolong life but it does not effect a cure

GLOMUS TUMOR (GLOMANGIOMA)

The treatment of glomus tumor is complete surgical excision under local infiltration or local nerve block

Tumors of Lymph Vessels

LYMPHANGIOMAS

Simple lymphangiomas may be excised if treatment is necessary Cavernous lymphangiomas may be treated by excision followed by the use of roentgen treatments or the implantation of radon seeds if the surgeon is not certain of complete removal of the lesion

Surgical excision is indicated for those cystic hygromas which are not too extensive Injection with 1–3 cc of 5 per cent solution of sodium morrhuate may be undertaken first Roentgen or radium therapy may be used as a final resort although the lesions are usually relatively resistant

Diseases of Capillaries (Increased Fragility)

PURPURAS DUE TO VITAMIN DEFICIENCY

Frank scurvy is not often encountered in clinical practice in the United States Vitamin C deficiency manifested by increased capillary fragility, impaired wound healing, and a reduced vitamin C level in the blood plasma is common and of considerable clinical significance Increased capillary fragility per se is not diagnostic

Angioneurotic Edema (Quincke's Disease, Giant Hives)

In general the excitants for angioneurotic edema are those which produce urticaria Although angioneurotic edema and urticaria are generally classified and discussed together, the two conditions rarely occur in the same individual

Symptomatic treatment consists of the administration of epinephrine or ephedrine as in urticaria The results are not likely to be successful in angioneurotic edema If the tongue, glottis, or pharynx is involved, the patient should be hospitalized so that tracheotomy may be performed promptly should the need arise Potential etiologic agents including foods, infection, drugs, and external contacts, should be sought and removed as far as possible Specific desensitization may be tried Nonspecific therapy is largely ineffectual

Sensitivity to Heat and Cold

These conditions have been discussed previously in the section on syndromes produced by temperature changes *

CIRCULATORY COLLAPSE

Vasomotor Collapse

Vasomotor collapse (primary circulatory collapse) is sudden and ordinarily short lived circulatory collapse It may occur, for example, in normal persons following psychic or physical trauma in injured or ill patients on mild exertion or on sudden change of position, and in the acutely ill when they are moved or handled When the peripheral circulatory failure, augmented by hemoconcentration and other factors persists as 'secondary shock,' the initial vasomotor collapse is commonly designated as 'primary shock"

Vasomotor collapse results from the pooling of blood in a dilated vascular bed and the blood volume need not be diminished The factors most often precipitating collapse are the loss of venous tone and the effect of gravity The loss of venous tone may be secondary to impulses arising in the central nervous system as a result of psychic stimuli, or it may be secondary to local causes such as the direct effect of the nitrites on the veins and venules

Collapse may occur upon change of position without any decrease in venous tone if the blood volume has been decreased by hemorrhage, dehydration or effusion Collapse may occur in the recumbent position as a result of serious peripheral circulatory failure, or because of powerful psychic stimulation in a susceptible individual Fainting may occur because of cerebral ischemia secondary to diminished cardiac output, or alkalosis secondary to reflex overbreathing (hyperventilation) or to a combination of these factors

The patient in circulatory collapse is placed in the recumbent position with his head at a level slightly lower than his feet A time honored method for restoring patients in whom the collapse is primarily psychic in origin, is to administer aromatic spirits of ammonia by inhalation Drugs are not often necessary because of the brevity of the usual attack, but 'paredrine in doses of 10–20 mg hypodermically, or paredrinol,' in doses of 25 mg parenterally, or 30–50 mg orally, are often effective in preventing or aborting attacks

The recovery phase will be accelerated if the patient is kept at rest and his warmth maintained by proper environmental temperature, by the application of blankets and by the administration of warm fluids by mouth In instances where pain is a factor, the administration of suitable analgesics is important In instances where apprehension and anxiety are factors mild sedation may prevent or minimize the severity of the reaction

Shock (Secondary Shock)

The treatment of secondary shock is discussed in Chapter 43

* See also Chapter 25

thrombocytopenic purpura is repeated blood transfusion followed by splenectomy. Treatment of the secondary form of thrombocytopenic purpura and of the nonthrombocytopenic symptomatic purpuras consists of repeated blood transfusion and specific treatment as far as possible of the primary disease. Measures directed to the support of the patient's nutrition and, consequently, to the integrity of his capillary endothelium ordinarily do not prevent capillary hemorrhages, although they may decrease the severity of the bleeding.

SENILE PURPURA

Purpura due to the loss of elasticity and lack of support of the smaller vessels by the skin and subcutaneous tissues occurs quite commonly in elderly and in debilitated persons. Nutritional deficiencies play a role in many instances. Preventive measures locally include the avoidance of trauma and the support of the flaccid tissues with elastic bandages. The existence commonly of multiple nutritional deficiencies indicates the need for careful dietary management supplemented by the administration of vitamins C and K, and, perhaps, rutin.

Diseases of Capillaries (Increased Permeability)

ALLERGIC REACTIONS

Urticaria (Hives, Nettle Rash)*

This cutaneous lesion is characterized by erythema, pruritus, and whealing. The wheals are due to serous exudation. The reaction which produces the wheal is ordinarily, an exaggerated response of the arterioles and capillaries to the influence of one or more of the following stimuli: infection by bacteria, protozoa, or metazoa; ingestion of certain foods or drugs, inhalation of pollens or dust, injection of drugs or biologicals, direct contact with external irritants, and physical agents.

Temporary relief from the eruption and the pruritus may be obtained promptly by the subcutaneous injection of 0.5 cc. of epinephrine (1:1000) or of 1.0 cc. of epinephrine in oil, or by the oral administration of 24 mg. of ephedrine.

"Benadryl" or pyribenzamine in doses of 50 mg. orally three times a day, or any one of the related antihistaminic preparations, will ordinarily provide symptomatic relief and may be used prophylactically. A copious intake of fluid is indicated to promote excretion, since eliminative measures are of some value in chronic urticaria.

To insure the patient adequate rest, one of the barbiturates, or chloral hydrate, or sodium bromide may be given at bedtime, but only after it has been shown conclusively that the drug does not precipitate attacks. Patients subject to recurrent attacks of urticaria should have 24 mg. enteric coated ephedrine tablets at hand, especially during the night for use should an attack occur. Local treatment with such antipruritics as plain or phenolated calamine lotion or tepid starch or soda baths often affords temporary relief.

they should be eliminated from the diet. If an infectious focus is discovered it should be removed surgically, or if this is not possible, by desensitization with an autogenous culture vaccine. Treatment with histamine, histaminase, 'hapamine,' calcium, peptone, allergosil, autohemotherapy, or by ultraviolet irradiation of the blood has been disappointing.

* See also Chapters 24 and 38

13. Anticoagulant Therapy

CHARLES D. MARPLE
& IRVING S. WRIGHT

ANTICOAGULANTS *are used primarily* to prevent or to retard the formation of intravascular thrombi and to minimize the hazard of embolization The use of the anticoagulants in the treatment of existing thromboembolic lesions is based likewise *on the ability of these drugs* to prevent—or to minimize—the occurrence of further thromboembolic complications whether extensions of the existing process or new thromboembolic lesions elsewhere in the body

Indications for the Use of the Anticoagulants

THERE are certain generally accepted *indications for the use of the anticoagu* lants There are also certain conditions in which the use of the anticoagulants has been reported favorably but not with suf ficient evidence to warrant unreserved rec *ommendation The indications for and pos sible uses of anticoagulant therapy are* enumerated in Table 12

CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

Numerous clinical reports epitomized by the experience of the American Heart Association s Committee for the Evaluation of Anticoagulants in Coronary Occlusion with Myocardial Infarction indicate that the administration of anticoagulants to persons immediately following acute coro nary occlusion with myocardial infarction will reduce significantly both the gross mor *tality and the morbidity from* thromboem bolic complications during the period of recovery and convalescence from the acute occlusion

The primary purpose of anticoagulant *therapy is to prevent the occurrence or minimize the effects of those thromboem* bolic complications which are now recog nized to be exceedingly common during the first four weeks following coronary *occlusion Preventing these complications* will reduce the gross death rate during this period by at least one third Anticoagulants will reduce the number of these complica tions by three fourths It is possible—but *unproved*—that anticoagulant therapy will modify the evolution of the coronary thrombus The use of anticoagulants ordi narily dicumarol, on a long term ambu

Burns*

Aside from the factors of immediate primary and secondary shock and of subsequent infection, burns are complicated by profound changes in the dynamics of the capillary circulation. Upon the proper management of this disturbed capillary circulation may depend the life of the patient.

There is increased capillary permeability which permits the loss of fluid and of protein. There is a decrease in the colloidal osmotic pressure resulting in a greater diffusion away from the capillaries. Fluid accumulation in the tissue spaces (edema) leads to an increased tissue pressure and an increased flow of lymph away from the burned area. The loss of fluid from the circulation into the burn site and from the body leads to hemoconcentration and a diminished plasma volume. The loss of protein into the tissue spaces and to the exterior leads to a decrease of circulating plasma protein and an increase in the lymphatic protein. Blood loss, aside from external bleeding, results from hemolysis of erythrocytes. Anemia and protein depletion interferes with hemopoiesis. Other vascular changes include widespread vasodilatation and a widespread stasis and thrombosis resulting directly from the burn and indirectly from shock.

Immediate Treatment. The immediate treatment is the management of shock. The patient is wrapped in a sterile sheet to minimize infection and covered with blankets. The temperature of the room is controlled. Morphine is given intravenously or subcutaneously to relieve pain. Fluids are administered parenterally. Whole blood is given in an amount equal to 2.5–5 per cent of the body weight to compensate for the immediate loss of red blood cell mass. Plasma and electrolytes are given as needed. Oral fluids may be given if tolerated and half strength Hartmann's solution or a solution containing 3 Gm. of sodium chloride and 1.5 Gm. of sodium bicarbonate per L. will aid in restoring normal electrolyte balance. Tetanus antitoxin is administered and burns of the eyes are treated to prevent corneal opacities. Oxygen is administered by nasal catheter or by BLB mask at a rate of 8 L. per minute to combat anoxia. When shock is controlled, the patient is removed to the operating room for treatment of the burned surface.

Supportive Treatment. The following measures are designed to support the patient after his return from the operating room to the ward. Make him comfortable in bed with any burned extremities elevated; administer analgesics, sedatives, and opiates as necessary to control pain, but do not depress respiration by giving large and frequent doses of morphine; continue oxygen therapy as long as it is necessary; continue the administration of fluids parenterally, determining the needs of the patient in terms of blood, plasma, and electrolytes by determining frequently the hematocrit, the hemoglobin and the red cell count, and by charting the patient's fluid intake and output; control infection by the use of appropriate antibiotics; observe the patient closely for the development of anemia, of acute massive edema, of laryngeal edema, and of severe infection; watch the urinary output since oliguria or anuria in the presence of an adequate fluid intake may indicate a lower nephron nephrosis.

A liberal fluid intake is maintained, by mouth when tolerated but parenterally if necessary. When the patient is able to ingest solid foods, he is encouraged to consume a diet rich in calories and in proteins. A supplement containing iron and vitamins is desirable and it is probably wise to administer vitamins parenterally each day until the patient is ingesting a full diet.

* See also Chapters 42 and 45.

hazard of fatal pulmonary embolism is *probably* greater when the thrombotic process involves the proximal portion of the femoral canal In cases of acute thrombophlebitis without embolism, in which the venous thrombus is probably well attached dicumarol' alone will almost invariably suffice

SUDDEN ARTERIAL OCCLUSION

Anticoagulants should be administered to all patients who suffer a sudden arterial occlusion, whether thrombotic or embolic, to prevent the propagation of the initial thrombus and to prevent the detachment of emboli If the occlusion is embolic in character, both heparin and dicumarol should be administered immediately, otherwise dicumarol alone is usually satisfactory

CHRONIC OBLITERATIVE ARTERIAL DISEASES

Anticoagulants should be administered prophylactically to patients with chronic obliterative vascular disease whose history includes or suggests a predisposition to thromboembolic phenomena Unless a thromboembolic complication has already occurred the patient should be given dicumarol and maintained on this drug over a considerable period of time to minimize the risk of repeated thromboembolic phenomena

POSTOPERATIVE AND POSTPARTUM USE

The prophylactic use of anticoagulants following surgical operations or childbirth is not warranted in all instances It is indicated under the following circumstances (1) the development of venous thrombosis (thrombophlebitis or phlebothrombosis) and/or pulmonary embolism (2) a history of thromboembolism or of a predisposition to thromboembolic phenomena, (3) extensive pelvic trauma (4) certain operations which are particularly conducive to thromboembolic complications such as major abdominal and pelvic operations (including major biliary tract surgery hysterectomies and gynecologic abdominopelvic surgery, intestinal resections and abdominoperineal resections, major genitourinary tract surgery, major thoracic surgery, radical mastectomies, and operative procedures on fractures) (5) operations upon patients over 40 years of age, (6) surgery in the presence of intraabdominal and certain other malignancies in which the incidence of thromboembolism is notoriously high

Gangrene of the Extremities

Anticoagulants may be indicated in the treatment of gangrene of the extremities whether posttraumatic, arteriosclerotic or diabetic, if a tendency to propagation of thrombosis is present The use of anticoagulants in the treatment of frostbite while theoretically sound has thus far proved disappointing in clinical practice

TABLE 13 CONDITIONS IN WHICH ANTICOAGULANTS MUST BE USED CAUTIOUSLY OR NOT AT ALL

1 *Prothrombin deficiency (hypoprothrombinemia)* or potential prothrombin deficiency
   a *Vitamin K deficiency*
   b *Severe hepatic disease*
   c *Idiopathic hypoprothrombinemia*
2 *Vitamin C deficiency*
3 *Renal insufficiency*
4 *Blood dyscrasias with impairment of the normal mechanisms for hemostasis*
5 *Interruptions in the continuity of the vascular system*
   a *Surgical operations*
      I Recent operations on the brain and spinal cord
      II Recent surgical operations leaving raw surfaces
      III Postoperative tube drainage of wounds or viscera
      IV Operations performed in the presence of obstructive jaundice external biliary fistula or severe liver damage
   b *Ulcerations and open wounds*
6 *Late pregnancy*
7 *Subacute bacterial endocarditis*

TABLE 12 INDICATIONS FOR ANTICOAGULANT THERAPY

INDICATIONS FOR ANTICOAGULANT THERAPY

1 *Pulmonary embolism due to an intravascular clot* to prevent further embolism which may be fatal
2 *Venous thrombosis (thrombophlebitis phlebothrombosis)*, to prevent further venous thrombosis and pulmonary embolism and to decrease the chances of chronic venous insufficiency
3 *Sudden arterial occlusion due to thrombosis or embolism*, to prevent propagation of a thrombus thrombosis at the site of an embolus or further embolization
4 *Traumatic injury to the blood vessel* to avoid thrombosis
5 *Postoperatively and postpartum* to prevent venous thrombosis and pulmonary embolism
6 *Coronary occlusion with myocardial infarction* to prevent thromboembolic complications
7 *Rheumatic heart disease with auricular fibrillation* to prevent embolization
8 *Gangrene of the extremities* to prevent local thrombosis and embolization
9 *Frostbite*[2]
10 *General vascular surgery* to prevent thrombosis and embolism at operation and postoperatively

CONDITIONS IN WHICH THE USE OF ANTICOAGULANTS HAS BEEN REPORTED FAVORABLY

1 *Chronic obliterative vascular diseases*[1]
2 *Mesenteric thrombosis*[3]

latory basis to prevent acute coronary thrombosis is still somewhat speculative since experience is limited and there is no statistical evidence to support the recommendation of such therapy

RHEUMATIC HEART DISEASE WITH AURICULAR FIBRILLATION

Wright and Foley have demonstrated conclusively that patients with rheumatic heart disease and auricular fibrillation who become invalids because of the frequent occurrence of arterial emboli originating from mural thrombi can lead completely normal, active lives when dicumarol is administered to them on a long term ambulatory basis Without anticoagulant therapy, these persons live in constant jeopardy of emboli to the pulmonary or systemic circulations While under the influence of properly managed and adequate dicumarol therapy the risk of embolization is reduced dramatically If such a patient is seen immediately following an embolic episode, he should be hospitalized and both heparin and dicumarol' administered immediately Heparin may be discontinued when the prothrombin time has become adequately prolonged

PULMONARY EMBOLISM

Anticoagulants should be administered immediately to patients who have suffered a pulmonary embolus to prevent or to minimize the chance of subsequent pulmonary emboli any one of which may be sufficiently massive to produce death There is little risk that a patient who develops a pulmonary embolus while under anticoagulant therapy will suffer a massive pulmonary hemorrhage Bloody sputum from an infarcted area constitutes a strong indication for rather than a contraindication to the use of anticoagulants Both heparin and dicumarol should be administered immediately to patients who have suffered a pulmonary embolus because of the immediate risk of secondary embolism When the patient's prothrombin clotting time has been prolonged satisfactorily heparin may be discontinued and the patient maintained on dicumarol

VENOUS THROMBOSIS (THROMBOPHLEBITIS AND PHLEBOTHROMBOSIS)

Anticoagulants should be administered to patients with thrombophlebitis or phlebothrombosis irrespective of the factors contributing to its development and of the general condition of the patient provided that none of the contraindications to be discussed subsequently are present Rapid heparinization is indicated in those cases in whom embolism has already occurred in whom the risk of embolization seems great or in whom there has been a rapid extension of the thrombophlebitic process The

response of the patient to this initial dose, 50 to 75 mg of heparin are administered intravenously every four hours thereafter and *the clotting time is determined imme diately preceding each subsequent injec tion* We believe that the clotting time should be determined on several occasions during each day until the response of the particular patient is clearly determined

Heparin in isotonic solution of sodium chloride in 5 per cent glucose solution or in distilled water may also be administered intravenously to bedridden patients by con tinuous drip The objective is to prolong the clotting time of the blood to two to four times normal and to maintain this prolongation for the duration of therapy This is generally achieved if 0 3–0 5 Gm of heparin is added to a liter of 5 per cent glucose and administered at a rate of 15 to 25 drops per minute for the entire twenty four hours From 15 to 25 mg of heparin are administered per hour and the total amount of fluid introduced in twenty four hours is about 1200 cc The clotting time of the whole blood should be deter mined ordinarily at intervals of every two to three hours since longer intervals with out testing are unsafe

If heparin is administered to a patient by this method immediately after opera tion the coagulation time should be deter mined every hour for the first twenty four hours because of the increased hazard of bleeding if the coagulation time is greatly prolonged The rate of flow of the infusion should be regulated carefully and fre quently

HEPARIN PITKIN MENSTRUUM

Heparin in Pitkin menstruum is dis tributed in ampuls containing 0 2 or 0 3 Gm of the sodium salt of heparin Ampuls labelled 'With vasoconstrictors contain ephedrine sulfate and epinephrine hydro chloride intended to delay absorption and thus prolong the anticoagulant effect The

use of heparin sodium 'with vasoco tors should be *avoided in patient* hypertension or myocardial diseas also in cases of arterial occlusi thrombus or embolus to avoid aggra the existing arterial spasm

We ordinarily administer an initi of 0 3 Gm of sodium heparin to p weighing up to 70 Kg and 0.4 Gm tients weighing more than this Subs doses are administered to maintai clotting time at between thirty and minutes by the Lee White method conventional dose of 0 3 Gm of h will be *satisfactory for about 90 pe* of patients The remaining 10 per ce either hypo- or hyperreactors and w quire doses of 0 4 and 0 2 Gm respec In the average patient a single dose 3 cc ampul containing 0 3 Gm he sodium will suffice to produce an ade heparin effect for approximately two To such a patient the content of one *ampul is administered every second d* the duration of therapy

If a blood transfusion is given th tient during this time one 3 cc amp heparin sodium in Pitkin menst should be administered immediately after irrespective of previous injectio the presence of a severe thromboem tendency 0 4–0 5 Gm of heparin i kin s menstruum is given and an att is made to prolong the clotting tir from one to two hours When vasocon tors are indicated and more than on pul is to be administered at a given use only one ampul of the combin The amount of vasoconstrictor dru one ampul is sufficient for an entire of heparin

In our experience heparin in P *menstruum is excessively painful and* patients frequently refuse a *second* tion Likewise the response of *the clo* time of the whole blood to this *form*

MESENTERIC THROMBOSIS AND EMBOLISM

The use of anticoagulants in mesenteric thrombosis and embolism is of particular interest because of the discouragingly high mortality rate in these conditions The chances of recovery when segments of the intestine have been deprived of their blood supply, either by occlusion of the mesenteric vessels or by strangulation, is very small unless resection is performed Heparin may facilitate a fatal outcome by promoting the escape of blood and fluid into the peritoneal cavity and into the bowel Since this may occur even after resection the postoperative administration of heparin must be carried out with the utmost caution

CONTRAINDICATIONS TO THE USE OF THE ANTICOAGULANTS

There are a limited number of circumstances in which the anticoagulants are to be used cautiously or not at all These are listed in Table 13

Administration of Heparin

HEPARIN is effective by all of the usual routes of parenteral administration

It has recently been reported that heparin is effective when administered sublingually, but careful studies in our laboratory at Cornell have not confirmed this claim The anticoagulant action of heparin is manifested by the prolongation of the coagulation time of the whole blood and its effect is measured with sufficient accuracy for clinical purposes by the determination of the clotting time of whole blood in a test tube, by the method of Lee and White

The advantages of heparin as an anticoagulant are (1) It may be administered by all of the various routes for parenteral administration—intravenously by intermittent injection or by continuous drip subcutaneously in aqueous solution or in a retarding menstruum intramuscularly in concentrated or dilute aqueous solution or suspended in oil or gelatin or intrasternally (2) Its effect in prolonging the coagulation time of the whole blood is prompt a matter of minutes and this effect, upon withholding the drug is promptly lost except when heparin has been administered in a menstruum which releases it slowly (3) The effect of heparin on the coagulation time can be determined conveniently at the bedside Heparin has two disadvantages which are definite handicaps to its use clinically It is expensive and is destroyed in the gastrointestinal tract

INTRAVENOUS HEPARIN

Heparin is commonly administered intravenously by the intermittent injection of the sodium salt dissolved in saline diluent in a concentration of 10 mg per cc Injections are made at intervals of from three to six hours most commonly at four hours

If a preliminary determination of the clotting time of the patient's whole blood reveals a normal value (four to eight minutes) 50 mg of sodium heparin in 5 cc of saline solution is injected intravenously and the clotting time is determined at intervals of approximately one hour for the first four hours The clotting time should be prolonged thirty to sixty minutes at the peak of effectiveness and it should not have returned to normal until three to four hours have elapsed Depending upon the

but it is available to qualified institutions for clinical trial Its principal advantage over heparin is its relative cheapness Certain lots of this substance have produced serious shocklike reactions and in some cases alopecia has developed some weeks after its use Judgment regarding its general clinical use must be deferred

Administration of "Dicumarol"

DICUMAROL has two great advantages over heparin It is cheap and it is effective orally There is no commercial preparation of dicumarol for parenteral administration

Dicumarol has certain disadvantages (1) Since a single dose does not produce its maximum effect as measured by the prolongation of the prothrombin clotting time for from forty eight to seventy two hours the patient to whom it is administered is not fully protected for this period of time following the initial dose For this reason when the immediate hazard of thromboembolism is great heparin should be administered concurrently for the first *two or three days to protect the patient* during this initial latent period (2) When dicumarol is withdrawn its effect on the prothrombin time persists for from two to seven days If a hemorrhagic complication occurs or if the anticoagulant effect of the drug must be terminated promptly for some other reason it is necessary to invoke *active measures* to antagonize the effect of dicumarol (3) The response of different individuals to given doses is not accurately predictable and the response of the same individual is often unpredictable from day to day, *necessitating the daily determination of the prothrombin clotting time before each dose of dicumarol is given*

When a patient who is receiving dicumarol has been under observation for a time and appears to respond in a reasonably *predictable manner it is frequently* possible to perform the prothrombin test *on alternate days and gradually, at longer* intervals up to one week The determination of the prothrombin time at intervals greater than every other day should not be attempted unless the physician has had an extensive experience with the drug Dicumarol requires painstaking and continuous supervision of the patient and of the *laboratory findings during the entire* period of anticoagulant therapy

DETERMINATION OF THE PLASMA PROTHROMBIN CLOTTING TIME*

The importance of the laboratory control of dicumarol therapy must be understood clearly by any physician who wishes to use the drug as an anticoagulant There are, in general two methods for performing the prothrombin test the one stage method or a modification thereof and the two-stage method The latter method is an excellent research tool but is not as widely used for clinical purposes as is the one stage method

The use of the one stage method for determining the prothrombin clotting time is complicated by several factors which *must be considered in the interpretation* of the results obtained The clinician must understand the test and the potential causes for the variations which may be encountered in order to interpret the values reported to him on samples of blood submitted from a given patient He must know what modification of the method is being used what thromboplastin is being

* See also Chapter 48

administration has been irregular and unpredictable

"DEPO-SOLUTION HEPARIN SODIUM"

Depo-Solution Heparin Sodium is a preparation of heparin sodium in a retarding menstruum of gelatin and dextrose It is distributed in 1 cc cartridges with disposable syringes each cartridge containing 0 2 Gm heparin sodium with or without vasoconstrictors The subcutaneous injection of two cartridges of depo solution heparin sodium one with and the other without vasoconstrictors deposits 0 4 Gm of heparin sodium and this dose is sufficient in most instances to produce an adequate anticoagulant effect for forty-eight hours More accurate control of therapy is attained by injecting 0 2 Gm (1 cc) of depo solution heparin sodium without vasoconstrictors at twelve hour intervals The clotting time determined just before a dose is to be given should not exceed twenty minutes If it does the dose should be postponed for six hours and the clotting time determined again before injecting more heparin

Depo solution heparin sodium has not proved in our hands to be a completely satisfactory long acting heparin It is distinctly less painful than is heparin in Pitkin menstruum but it is difficult to predict its action in different individuals or in the same individual at different times

CONCENTRATED AQUEOUS HEPARIN

Heparin may be administered intramuscularly dissolved in an aqueous medium for prompt absorption or suspended in an oily menstruum for delayed absorption It is claimed that these injections are less painful than is the injection of heparin in Pitkin menstruum Intramuscular injection is preferred not only because it is less painful than is subcutaneous injection but because absorption is more regular The paucity of reports on clinical experience with the intramuscular injection of dilute heparin suggests that the experience with it has been unsatisfactory A disadvantage is that a relatively large volume of solution must be injected with each dose since each cubic centimeter of solution or suspension contains only 10 mg of heparin

A concentrated solution of heparin containing 0 1 Gm heparin per cc. has been administered successfully by intramuscular injection This preparation free of vasoconstrictors or foreign substances fulfills the requirements for simple, painless safe, and readily controlled administration The concentrated heparin is injected into the gluteal muscles at intervals of from eight to twelve hours A prolongation of the coagulation time is evident within half to one hour after the initial injection reaches a maximum (thirty to sixty minutes) in from four to six hours after injection and approaches normal in about eight to twelve hours after injection

Individual doses of concentrated aqueous heparin vary from 50 to 180 mg correlating roughly with the weight of the patient Adequate heparinization of patients weighing less than 52 Kg is attained by the injection of 0 1 Gm every eight hours or by the injection of 0 12–0 14 Gm every twelve hours Proportionately larger doses are used for heavier individuals The maximum daily dose should not exceed 0 35 Gm

SUBSTITUTES FOR HEPARIN

Paritol an alginic acid compound with properties not unlike those of heparin is being investigated currently Its administration parenterally produces a similar prolongation of the clotting time of the whole blood The greatest amount of experience with this agent has been acquired by Sorenson and his co-workers The drug is not yet generally available commercially,

should utilize a prothrombin activity curve constructed by the particular laboratory according to the method, technic, and thromboplastin ordinarily employed

Such a curve is constructed as follows Samples of normal whole plasma are diluted to *50 per cent, 25 per cent, 12 5 per cent*, and 6 25 per cent with saline, and the prothrombin time determined for each dilution These are then *plotted on a graph*, the ordinates of which are the prothrombin times in seconds the abscissae, the prothrombin activity in percentages of normal Fig 7 shows a typical example of such a prothrombin activity curve It is to be noted that this is a hyperbolic curve It represents the relationship between pro*thrombin time and per cent of prothrom*bin activity obtained in a particular laboratory, using a particular method, a consistent technic, and a thromboplastin prepared, in this instance from rabbit lung It applies only if these considerations are met and, in this example if the prothrombin time obtained with normal whole plasma falls within the range of 15–17 seconds

The laboratory should report to the physician (1) *the prothrombin activity of the* patient s plasma as a percentage of normal, (2) the prothrombin time of the patient s plasma, and (3) the prothrombin time as determined on normal plasma on that given day If the normal control for *the day is outside the range ordinarily ob*tained by the laboratory, the test should be repeated with a new batch of thromboplastin In all instances, providing the physician with the normal or control' value *for the day* assures him that the report is founded on an accurate base line

A report of the patient s prothrombin time in seconds *is an additional means for* comparison with the report of the previous day We advise further that all reports be entered graphically or in tabular form *on a* single sheet in the patient s hospital record as this is often valuable in evaluating the prothrombin record

With these considerations in mind dicumarol is *administered as follows A pro*thrombin time is always determined before giving the drug If the initial prothrombin *time is normal*, the initial dose of dicumarol is between 0 2 and 0 3 Gm Thereafter, the prothrombin time is determined *on each day before* any 'dicumarol is given The ideal reduction in prothrombin activity is to between 10 and 30 per cent of normal and the activity should be maintained within this range as far as possible As a rule, the dose of 'dicumarol' on a given day will bear a relationship shown in Table 15 to the prothrombin activity of *the patient s plasma on that day*

TABLE 15 PERCENTAGE PROTHROMBIN *ACTIVITY AND USUAL DICUMAROL DOSE*

Prothrombin activity (% Normal)	*Dose of dicumarol indicated*
300–100	100–200 mg
15– 30	50–100 mg
10– 15	0– 50 mg
<10	0

No more exact dosage schedule can be recommended since the response will vary not only from patient to patient, but in the same patient from day to day *depend*ing on the prothrombin level and on the influence of previous doses of dicumarol

The dosage is modified frequently according to the trend in the prothrombin clotting time on a given day A smaller dose of 'dicumarol given during a period in which the prothrombin clotting time is becoming longer will usually have an effect equal to that produced by a larger dose of dicumarol administered while the prothrombin time is becoming shorter An occasional patient, the hyporeactor, may require doses of 0 2 Gm of dicumarol al*most every day to reach* and maintain the desired prolongation of the prothrombin

TABLE 14 CONVERSION TABLE FOR PROTHROMBIN TIME*

Prothrombin time (sec)	Prothrombin activity (% normal) Quick's method	Link-Shapiro method
11–13	100	—
15	50	100
17	40	—
19.5	30	50
24–26	20	30
29	15	20
37	10	—
40	—	10
55–65	5	—

* Relationship between prothrombin time in seconds and degree of prothrombin activity as a percentage of normal as determined by Quick's original one stage method and by the Link Shapiro modification of this method

used, and what value is obtained when the prothrombin clotting time of whole normal plasma is determined daily as a control

Reference to Quick's Method should indicate the one stage method described by A J Quick and the utilization of a thromboplastin prepared from rabbit brain Reference to the Link Shapiro Method' should refer to a modification of Quick's method in which a thromboplastin prepared from rabbit lung is used and a somewhat different technic employed The prothrombin times obtained by these different methods with given specimens of plasma will vary considerably over the higher ranges of plasma prothrombin activity, as demonstrated in Table 14 and in Fig 6 Thus in determining the prothrombin time it is essential to know what method is being used

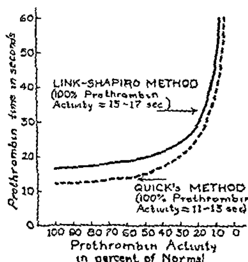


FIG 6 Variations in the relationship between prothrombin activity (in percentage of normal) and prothrombin time (in seconds) when the latter is determined by two different methods

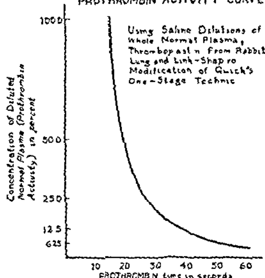


FIG 7 Typical hyperbolic prothrombin activity curve constructed by determining the prothrombin times obtained with saline solutions of whole normal plasma by the Link-Shapiro modification of the one-stage method

In order to reduce the values obtained to a common denominator, i e, to permit comparison between values obtained by these different methods, it is customary to convert the prothrombin time in seconds to prothrombin activity as a percentage of normal It is incorrect to do this by dividing the prothrombin time of the normal by that of the unknown To convert prothrombin time to the degree of prothrombin activity in percentage, the laboratory

trauma may produce an unusual amount of bleeding

Long term "dicumarol" therapy has permitted most of the patients so treated to lead fairly normal lives and to continue, when necessary, at a gainful occupation There have not been any serious hemorrhagic complications reported when such therapy has been prescribed carefully, but the method requires constant vigilance on the part of the physician and faithful cooperation on the part of the patient and his family

SUBSTITUTES FOR DICUMAROL

Several potential substitutes for "dicumarol" are being investigated currently These include "tromexan," phenylindanedione and 4 hydroxycoumarin No 63

Tromexan

"Tromexan" offers a definite advantage over "dicumarol" in that its effect is exerted promptly following administration An initial dose of "tromexan" will usually produce a prolongation of the prothrombin time within eight to sixteen hours and its effect reaches a maximum in from twenty four to thirty six hours "Dicumarol," as noted previously, does not produce its maximum effect for from forty eight to seventy two hours

The effect of "tromexan" wears off rapidly This is important in two respects (1) the effect of the drug unlike that of "dicumarol," tends not to be cumulative and (2) when "tromexan" is discontinued, the relatively prompt loss of its effect decreases the risk of hemorrhage

The greatest experience with "tromexan" in this country to date has been accumulated by Irving S Wright and his associates at the New York Hospital They have administered "tromexan" in an initial dose of 1 5–1 8 Gm and followed this with divided daily maintenance doses of 0 6–0 9 Gm "Tromexan" may be used clinically as a substitute for "dicumarol" and may prove to be a more satisfactory anticoagulant Some workers have had difficulty in regulating the prothrombin activity in a satisfactory manner, but our experience would lead us to believe that this is related to lack of practice with this new drug

Phenylindanedione

Phenylindanedione has been used clinically by Blaustein, who recently reported on its use in 53 patients He concluded that initial doses of 0 2 Gm are adequate and that the average daily maintenance dose is in the neighborhood of 65 mg There has not been sufficient clinical experience with phenylindanedione to warrant its general use at the present time

4 Hydroxycoumarin No 63

The compound 4 hydroxycoumarin No 63 has been reported as a potential substitute for "dicumarol" Experiments on animals indicate that the degree of anticoagulant action can be greater and its duration longer than that of "dicumarol" without producing hemorrhagic manifestations Further experience with this agent is necessary before its role in anticoagulant therapy can be assessed

clotting time Hyperreactors encountered not uncommonly among patients with renal insufficiency, severe liver damage, or congestive heart failure, may not require more than 50 mg a day Far better results are obtained by giving smaller doses every day than by giving massive doses on two or three days out of each week If the prothrombin clotting time is prolonged beyond sixty seconds, the risk of hemorrhage is real

'Dicumarol is administered to the majority of our patients for twenty to thirty days after the last episode of thrombosis or embolism.

The prothrombin clotting time of the patient s plasma diluted to 12 5 per cent with saline solution may be determined each day and reported along with the prothrombin clotting time of the whole (undiluted) plasma The greater sensitivity of the dilute plasma in reflecting changes in the prothrombin activity of the plasma is frequently of value in deciding upon the daily dose of dicumarol The effect of dicumarol on the prothrombin activity of the plasma may be evident as much as a day earlier when 12 5 per cent is used than when whole plasma is used

As mentioned previously if there is an urgent need for an immediate anticoagulant effect, heparin may be administered concurrently with dicumarol until the prothrombin time has been prolonged to the equivalent of a reduction in prothrombin activity to 30 per cent Heparinization does materially influence the prothrombin time if the coagulation time of the whole blood is elevated appreciably Samples of blood for the determination of the prothrombin time should be drawn from the patient just before a dose of heparin is to be given Dicumarol does not ordinarily prolong the coagulation time of the whole blood as determined in glass tubes If the physician and laboratory work as a team there is rarely difficulty in managing the administration of either drug

LONG TERM ANTICOAGULANT THERAPY

It is advisable to continue anticoagulant therapy for an indefinite period in those patients who have suffered repeated thromboembolic episodes as a result of rheumatic heart disease with auricular fibrillation, or of acute coronary occlusion with myocardial infarction

These patients are hospitalized for a minimum of three weeks and dicumarol therapy is carried out in the conventional manner to determine the patient s response to dicumarol and to set a pattern for its administration The aim of long term dicumarol therapy is the same as that of the conventional treatment to prolong the prothrombin time of the whole plasma to between twenty five and thirty seconds (i e to reduce the prothrombin activity to between twenty and thirty per cent of normal) and the details are the same If the patient s daily requirement for dicumarol is fairly constant he can be sent home on a specified daily dose of the drug with instructions to report twice a week for a prothrombin determination If the prothrombin level shows only minor fluctuations the interval of time between prothrombin determinations may be extended to a week It is rarely advisable to extend the interval between prothrombin determinations beyond this

Since this method of management is somewhat hazardous it is extremely important that the patient be intelligent and cooperative and that he take the exact amount of dicumarol prescribed and appear regularly for prothrombin determinations He should be warned to report immediately to his physician any hemorrhagic manifestations or other change in his physical condition He should also be made aware of the possibility that mild

TREATMENT OF HEMORRHAGE AND OF EXCESSIVE HYPOPROTHROMBINEMIA DUE TO DICUMAROL

Use of Blood Transfusions

When it is desirable to reduce an excessively prolonged prothrombin time or to staunch bleeding which occurs as a result of hypoprothrombinemia the transfusion of 500 cc of fresh whole blood which may be citrated is usually effective temporarily Banked blood which has been stored for more than twenty four hours is usually less effective than fresh blood Since the prothrombin time tends to increase again in from two to six hours after a transfusion of fresh blood it is usually necessary to administer transfusions repeatedly over a period of several days in order to control bleeding or to permit the prothrombin level of the blood to return to normal

Use of Lyophilized Plasma

Lyophilized plasma reconstituted with 0.1 per cent citric acid and distilled water possesses a normal prothrombin content comparable to that of fresh whole blood It has the advantage over whole blood of not being diluted to approximately 50 per cent with cellular elements

Lyophilized plasma is effective in reducing the prothrombin time immediately While lyophilized plasma may serve to maintain the prothrombin time within a safe range temporarily until a normal prothrombin activity is restored by the use of vitamin K or through spontaneous recovery of prothrombin synthesis pooled lyophilized plasma should be used only when grouped fresh blood is not available due to the risk of transmitting homologous serum hepatitis

Use of Vitamin K *Preparations*

It has been demonstrated repeatedly that the synthetic naphthoquinones do not usually either diminish the degree, or shorten the duration of the hypoprothrombinemia resulting from dicumarol when they are administered orally or parenterally, in the doses employed successfully in the treatment of ordinary vitamin K deficiency It is well established clinically, however, that when preparations possessing vitamin K activity are administered in large doses they will usually counteract the hypoprothrombinemia and control the bleeding due to dicumarol

The minimum single dose of the synthetic vitamin K preparations necessary to exhibit this effect consistently is in the range of 64 to 75 mg depending upon the preparation used It must be given intravenously to assure prompt action The patient s condition and his prothrombin clotting time must be checked at frequent intervals and additional doses of similar magnitude administered at four hour intervals until the response is satisfactory Repeated doses of the vitamin K preparations totalling 0.5–1.0 Gm have been given clinically without apparent ill effect

When the prothrombin time of patients receiving dicumarol becomes excessively prolonged (below 10 per cent of normal) 30 to 60 mg of menadione bisulfite may be given intravenously and subsequent doses of ' dicumarol ' reduced in amount or omitted If bleeding of a significant degree occurs 60 mg of menadione bisulfite may be given intravenously and followed immediately by a transfusion of 500 cc whole fresh blood

Recently it has been found that vitamin K_1 and vitamin K_1 oxide will restore the prothrombin time rapidly to normal when given in doses of 0.25–0.5 Gm either parenterally or in capsule form The effect is more specific than that of the water-soluble substances but it has the disadvantage that coumarin derivatives may not be capable of prolonging the prothrombin time again for several days

Management of Hemorrhage Due to Anticoagulants

HEMORRHAGE is the only common complication of anticoagulant therapy irrespective of whether heparin or dicumarol is employed Other complications are rare and ordinarily of slight clinical significance

Bleeding occurring during or after the administration of heparin or dicumarol is frequently unpredictable It may occur when, in the case of dicumarol the prothrombin clotting time is not prolonged excessively and when in the case of heparin the coagulation time of the whole blood is within the range recommended for therapeutic effect When bleeding is encountered under these circumstances a careful search often discloses a previously unrecognized pathologic condition such as a malignant tumor or an ulceration which explains the unexpected bleeding It may occur in patients who do not exhibit any condition predisposing to hemorrhage and in whom even the most painstaking study fails to reveal an explanation

The incidence of hemorrhagic complications following the administration of anticoagulants is significantly greater where the physician s experience with this type of therapy is limited and where the laboratory and clinical management of the therapy is less than exacting In brief except in rare instances serious hemorrhages and fatalities due to hemorrhage are a result *of incompetent administration* erroneous laboratory reports or of lapses in an otherwise meticulous regimen

Satisfactory treatment of serious bleeding depends upon efficient emergency management of the immediate situation This includes the immediate discontinuance of the anticoagulant the administration of whole blood to replace blood loss and to combat shock the use of ancillary measures to support the patient and the administration to the patient of adequate amounts of the specific antagonist effective against the particular anticoagulant being used

TREATMENT OF HEMORRHAGE DUE TO HEPARIN

The first step in controlling a significant amount of bleeding due to or aggravated by heparin is to withdraw the drug Transfusions preferably of whole fresh blood may be given to restore blood loss and to stimulate blood coagulation Citrated blood may be used but it should be fresh

There are available two substances which exert a specific antagonism to the anticoagulant effect of heparin These are the azo dye toluidine blue and the protein from fish roe, protamine sulfate Either may be administered intravenously in doses of 1–4 mg per kg body weight Both act promptly in restoring the coagulation time of whole blood to normal but their effect may be transient and repeated injections on subsequent days may be necessary It is advisable to determine the clotting time of the whole blood at frequent intervals until it has become normal and remained so for a period of several days

Toluidine blue or protamine sulfate are usually well tolerated when administered intravenously in man although some toxic reactions have been reported following the latter A dose of about 2 mg per kg body weight appears to be adequate with either drug They are ordinarily administered intravenously over a two-hour period in 250–500 cc normal saline

Neither toluidine blue nor protamine sulfate is effective when administered orally Both substances should be used with caution at the present time since clinical experience with them is limited

14. Blood Diseases

ROY R. KRACKE
& STEVEN O. SCHWARTZ

Anemia

DEFINITION

The term *anemia* in this chapter refers to the generally accepted clinical concept of a quantitative reduction below normal in the values of hemoglobin, and usually of the red cells. Practical clinical measurements are concerned with the concentration of oxygen-carrying red cells, hemoglobin, and packed red corpuscles in a unit of volume of blood. Anemia, then, is the condition that results when there is a diminution from normal in the number of red corpuscles per cubic millimeter, in the amount of hemoglobin and in the volume of packed red cells per hundred cubic centimeters of blood.

CLASSIFICATION

Because the concern here is with therapy and not with nomenclature or the rationale of the various nosologic preferences, systems of classifying types of anemia are not considered. It should be sufficient to indicate that the various common types of anemia are here designated for practical convenience by their generally accepted descriptive terms, whether their basis is morphologic or derived from Wintrobe's concept of the *erythron* as an organ consisting of the circulating red corpuscles as well as the marrow from which they derive which, as an organ, may atrophy or hypertrophy, may be impaired by infections and toxemia, is susceptible to congenital dystrophies and to pathologic changes manifested in acute or chronic blood loss, blood destruction, decreased production of blood as a result of nutritional deficiency, inhibition of blood-forming organs, and trauma.

There are other types of anemia which do not fall into large divisions but occur in association with other diseases as the underlying cause. Some of these types of anemia and still others are not amenable to treatment under our present understanding and are, therefore, grouped under *Refractory Anemias*.

For purposes of treatment the anemias may be subdivided as follows:

I. Anemia Secondary to Other Diseases
II. Iron Deficiency Anemias
   Idiopathic Hypochromic Anemia
III. Macrocytic Anemias
   a. Pernicious Anemia
   b. Sprue
   c. Fish Tapeworm Disease
   d. Liver Disease
   e. *Achrestic Anemia*
   f. Miscellaneous Macrocytic Anemias
   g. Pellagra

The vitamin K preparation should be repeated at regular intervals of four hours until the prothrombin time has returned to and been maintained at approximately normal Transfusions may be given periodically to control the bleeding and to combat any anemia

The risk of administering 'dicumarol' to women late in pregnancy is not only that the mother may bleed profusely at the time of delivery, but that the infant may suffer severe hemorrhages either during or following birth It is suggested that when 'dicumarol' is administered to a pregnant woman at term, it be withheld from the time the patient goes into labor and that with the onset of labor, the patient be given large doses of a vitamin K intravenously, repeated as often as indicated by the patient's prothrombin time Following delivery the mother may again be placed on 'dicumarol' if necessary Immediately after delivery and periodically through the first week of life the infant should be given vitamin K parenterally

increase between 300 000 and 500 000 cells per cubic millimeter per week, their rise being inversely proportional to the severity of anemia

It is never necessary to treat pernicious anemia with *oral preparations* of liver extract Nearly all patients can take liver extract by injection without reactions, although about 10 per cent of patients eventually *develop sensitivity The allergic* symptoms can be relieved or prevented by the subcutaneous administration of 0 5 cc *of 1 1000* solution of epinephrin Prominent signs and symptoms that accompany such reactions are flushing palpitation, and tachycardia, sometimes generalized itching of the skin, and urticaria Occasionally there may be loss of consciousness The reactions may occur in patients who have been taking liver extract satisfactorily over a long period Desensitization of the patient can be tried by giving a subcutaneous injection of 0 1 cc of 1 10 dilution of liver extract and increasing this about 0 2 cc every two or three days for about three weeks until the patient is receiving the full therapeutic dose The patient can be kept desensitized by giving the therapeutic dose in smaller quantities and at more frequent intervals *A simpler expedient is to change to* vitamin B_{12} using 1 μg as the rough equivalent of 1 unit of liver Patients may develop sen*sitivity to the* '*crude vitamin* B_{12} *in* which case the crystalline substance can be used

IRON *It is seldom necessary to give iron* to patients with pernicious anemia

TRANSFUSIONS Occasionally it may be necessary to give blood *transfusions when* the patient's condition is poor or complications are present

DIET The diet should be abundant The patient may eat whatever he wishes but the diet should include ample protein in the form of meat, eggs and milk Consumption of liver is desirable but not necessary

HYDROCHLORIC ACID It is not necessary to give dilute hydrochloric acid although occasionally considerable subjective relief may follow its use

ADJUNCTS In cases of advanced neurologic disease, the patient may be unable to void and it may be helpful to introduce a catheter *into the bladder If this is done,* antibiotic drugs should be given to prevent infection Depending on the severity of *neurologic changes* physiotherapy is a useful adjunct for patients with cord degeneration Precisely what should be done varies with different patients active and passive exercises, occupational therapy and massage are sometimes beneficial

Every effort should be made in all instances to have the patient ambulatory

Prognosis The life expectancy of patients with pernicious anemia is about the same as that of normal persons so long as the patient receives adequate therapy and has no irreversible neurologic complications Even patients with neurologic disease under careful supervision and with adequate therapy, will live comfortably for many years

b Sprue Sprue resembles pernicious anemia It is a chronic wasting disorder in which there is glossitis diarrhea and the passage of light-colored, bulky, and frothy stools It was formerly thought to be limited to the tropics where it is endemic, but it *has been reported in* milder form in temperate zones and countries as far north as Scandinavia as well as in the north of the *United States*

The macrocytic anemia of sprue is best treated by the oral use or injection of folic acid *In acutely ill patients* this can be done by daily intramuscular injection of from 10–15 mg of folic acid This is fol*lowed by a rise in reticulocytes* and a return of the megaloblastic marrow to a normal pattern and a rise in hemoglobin and *red cells to normal levels It is* also accompanied by improvement in strength and a sense of well being There is increased

IV Hemolytic Anemias
  a Congenital Spherocytic Anemia
  b Acquired Hemolytic Anemia
    1 Acute Idiopathic Hemolytic Anemia
    2 Hemolytic Anemia Caused by Chemicals and Drugs
    3 Hemolytic Anemias Caused by Infections
  c Erythroblastosis Fetalis
  d Mediterranean Anemia
  e Sickle Cell Anemia
  f The Hemoglobinurias
V Aplastic Anemia
  a Idiopathic Aplastic Anemia *Osteosclerosis*
  b Secondary Aplastic Anemia
VI Anemias of Pregnancy
VII Refractory Anemias

TREATMENT

In the treatment of the many kinds of anemia there must always be one governing principle the understanding of etiology There is no such thing as a method of treating every type of anemia no single drug that will remedy all varieties of anemia, no combination of substances that cures anemia in all its forms Before treatment is begun etiology must be established In most cases the etiology will be apparent from the history and examination in others valuable clues will be found in the blood whereas in an occasional case chemical studies marrow examination and other accessory means of investigation will be needed to uncover the underlying cause

Any approach other than etiologic will be not only unscientific and unsound but wasteful of time effort, medication and money

I Anemia Secondary to Other Diseases

Anemia secondary to other diseases is often referred to as *simple chronic anemia* This is the term preferred by Wintrobe because formerly 'secondary anemia included all types of anemia other than the pernicious variety The term is also descriptive since simple chronic anemia shows no great departure from normal blood has an insidious onset and its reparative course is slow unless the associated disease is cured This type of anemia, however, is secondary in that it does occur in association with other disorders such as chronic infectious diseases malignancies inadequate diet vitamin deficiencies intestinal parasitism and diseases of the kidney and liver A severe form is seen following acute blood loss but ordinarily the anemia is mild chronic in course and consists of a simple reduction in the number of red cells with a corresponding reduction in hemoglobin

The treatment of this group type of anemia consists almost entirely of removal or correction of the fundamental cause This entails search for foci of infection or for parasites in the intestinal tract the demonstration of underlying pathologic states and the evaluation of the diet Hematinics are of no value unless these primary conditions have resulted in either iron deficiency from chronic bleeding or in deficiency of the liver extract principle due to inadequate food intake or absorption Transfusions of blood may be necessary if anemia is unusually severe as in far advanced cases of malignancy or intestinal parasitism as well as when it is necessary to replace acute massive or protracted loss of blood

It is emphasized that unless the cause can be found and eliminated, anemia will persist.

II Iron Deficiency Anemia

Iron-deficiency anemia is common Characteristically the red cell contains less than the normal amount of hemoglobin and therefore becomes microcytic and hypochromic. This type of anemia in the adult is a consequence of chronic bleeding inadequate iron intake or improper absorption In childhood the commonest causes are prematurity, iron deficiency in the

should be carefully evaluated periodically after operation because in addition to anemia, an iron deficiency state often results in suboptimal health and inadequate functional integrity of the upper part of the intestinal tract

The megaloblastic anemia of infancy accompanied by macrocytic anemia has been ascribed to infections and nutritional deficiencies and also to dietary deficiency in the mother Macrocytic anemia in the newborn may not be due to deficiency of the antipernicious anemia principle—as Wintrobe has pointed out—but rather to the numerous *immature cells that* are present In such instances liver therapy is ineffective Megaloblastic anemia of infancy accompanied by macrocytic anemia may be corrected by the administration of folic acid in daily doses of 5 mg which can be incorporated in the feeding formula If the condition is severe transfusions of blood (25–50 cc) may be necessary Neither liver extract nor vitamin B_{12} are so effective as folic acid

When *macrocytic anemia accompanies hypothyroidism,* the employment of thyroid extract results in a slow amelioration of the condition It is well to administer thyroid in increasing doses beginning with 30 mg daily until optimal levels ranging from 120 mg to 250 mg daily are reached *

g Pellagra Some patients with pellagra will exhibit macrocytic anemia Anemia in such instances responds either to the administration of folic acid by mouth or to the injection of adequate amounts of liver extract, on a regimen similar to that recommended for sprue *More important* however is the correction of the diet which should be particularly high in meat milk cheese eggs, and butter Inasmuch as the disease is primarily a deficiency of the extrinsic (dietary) factor and many of its symptoms are caused by vitamin deficiency adequate amounts of nicotinic acid and other vitamins of the B group should likewise be administered

* See also Chapter 29

IV Hemolytic Anemias

Clinically, hemolytic anemias are subdivided into *hereditary*, such as the spherocytic target cell and sickle cell types and *acquired* (secondary to coexisting disease) which may be idiopathic or symptomatic namely the hemoglobinurias, which are fulminant variants of the hemolytic anemias are commonly classed as cold ' nocturnal march and other minor types

Several theories have been offered to explain the pathogenesis of hemolytic anemias It is probable that the syndromes are the result for the most part of several factors which although acting singly on occasion usually act in combination These factors are defective red blood cell formation abnormal function of the reticuloendothelial system and the spleen erythrostasis in the spleen with consequent agglutination and a resulting destruction of erythrocytes or the abnormal production of agglutinins and hemolysins The most attractive of these theories is that of excessive hemolysin production for which clinical and experimental corroboration have been found

Hemolytic anemias have certain characteristics in common A hemolytic anemia is one in which the red cells have a shorter life cycle than the normal span of 100–120 days If the rate of cell destruction exceeds the rate of production then anemia develops On the other hand if red cell production is able to keep pace with destruction anemia may not develop even though active hemolysis is taking place

When red cells are destroyed in excessive numbers an increased amount of bilirubin is present in the plasma and increased urobilinogen and urobilin in the urine and stools The pigment may be sufficiently increased to result in visible jaundice on the other hand it may not be demonstrable

appetite, gain in weight, and decrease of diarrhea, with disappearance of glossitis associated with regeneration of papillae of the tongue After disappearance of the gastrointestinal symptoms the drug may be administered by mouth rather than by injection, apparently with equally good results

Sprue can also be treated with injectable liver extract in adequate dosage (15 units daily) following the regimen outlined for pernicious anemia The cruder liver extract seems superior

The treatment should include a high vitamin and high protein diet which is liberal in the use of meat milk eggs, and cheese

c Fish Tapeworm Disease Infestation with the fish tapeworm causes macrocytic anemia * This type responds best to treatment of the parasitic disease itself although anemia may be ameliorated by the use of intensive treatment with injectable liver extract

d Liver Disease The symptoms of macrocytic anemia in association with liver disease are clinically those of liver disease itself † Deficient diet, faulty absorption and a variety of other abnormalities appear to be contributory causes of macrocytic anemia along with the liver disease which may or may not be fundamental to the disorder The incidence is still controversial and the etiology is variously explained Presumably macrocytic anemia in this group develops because of the inability of the liver to produce the hematopoietic factors properly On the other hand, some investigators have demonstrated the presence of these factors in patients dying of liver disease The disorder has also been ascribed to defective storage of the antipernicious anemia principle but numerous dissimilarities to pernicious anemia make this thesis untenable

* See also Chapter 9
† See also Chapter 17

Treatment is based on an attempt to correct the liver disease rather than on treatment of anemia Liver extract therapy is rarely effective

e Achrestic Anemia An occasional instance of macrocytic anemia has been reported in which the observations are similar to pernicious anemia except that there is free hydrochloric acid in the gastric contents and the patient fails to respond to antipernicious anemia therapy Furthermore, it has been demonstrated that the hematopoietic principle is present in the liver It was on the former assumption that the antipernicious anemia principle could not be utilized that the disorder was termed *achrestic* from the Greek negative prefix *a* and *chresis*—' use ' The symptoms are chiefly those of the anemia itself

Achrestic anemia is one of the refractory types of anemia resembling ' progressive hypocythemia" described by Thompson The disease is fatal, although blood transfusions and intensive liver therapy may prolong life

f Miscellaneous Macrocytic Anemias The treatment of other macrocytic anemias including those secondary to intestinal strictures, gastric resections, idiopathic steatorrhea, tropical macrocytic anemia, and marrow lesions consists primarily in correction of the underlying disease For the most part these conditions respond as well or better to folic acid (10–15 mg by mouth daily) as to liver extract This measure simply corrects the hematologic deficiencies however In most of these conditions, anemia will be refractory to treatment, especially if the causative disease cannot be successfully controlled

Patients who undergo extensive surgical operations on the stomach must be observed indefinitely to anticipate, if possible, or at least to correct in its incipiency the development of severe macrocytic anemia and the accompanying neurologic degeneration Not only the diet but its utilization

vent reactions Splenectomy may be of value but its efficacy cannot be foretold with certainty, therefore every effort at con servative management should be exhausted before resorting to surgery

Hormone therapy has given encouraging results and usually deserves trial The use of corticotropin intravenously and intra muscularly has given better results than the use of cortisone Often it is possible to tide the patient over an acute crisis with these agents, permitting the process to subside spontaneously or allowing splenectomy to be performed

Acute idiopathic hemolytic anemia Acute idiopathic hemolytic anemia, some times referred to as the Lederer type, is seen at all ages but more frequently in young people, and is characterized by signs of sudden increased destruction of large amounts of blood It is not necessarily char acterized by spherocytosis or increased fra gility of red cells It is treated entirely by blood transfusions repeated often enough to maintain normal cell values Recovery usually follows There is no indication for splenectomy in this syndrome

Hemolytic anemia caused by chemicals and drugs It is well known that acute epi sodes of hemolytic anemia may be caused by the ingestion of or exposure to various toxic agents chemicals and drugs These include such agents as phenylhydrazin or acetylphenylhydrazin, the sulfonamide drugs, methyl chloride, colloidal silver, trinitrotoluene dinitrobenzol, aniline, amido compounds and nitro compounds of phenol, benzene, toluene, lead, acetanilid, nitrites, and probably a great many others If a patient develops either an acute or chronic episode of hemolytic anemia, it is important that a careful history be obtained of ingestion of or exposure to any of these agents The most important therapeutic measure, therefore, is the removal of the patient from further exposure Anemia usually corrects itself once the agent is re moved Occasionally, when severe anemia ensues, transfusions of blood may be necessary

Hemolytic anemia caused by infections It is known that varying degrees of hemo lytic anemia may be produced by infections bacterial toxins, viruses, and other agents that produce acute febrile diseases These include the toxin of gas gangrene, infesta tion with the malarial parasite, Bartonel losis, various bacterial toxins, especially those of *Cl welchii*, *S pyogenes*, and *S vir idans*, viruses as in virus pneumonia, vege table poisons as in favism, animal poisons such as snake venoms

Treatment once again ordinarily consists in treating the disease rather than the anemia, thereby correcting the anemic condition, however, if treatment of the anemia *per se* is required, it can and should be done only by blood transfusions None of the hematopoietic agents is of service in the treatment of any type of hemolytic ane mia, whether acute or chronic, acquired or congenital

c. **Erythroblastosis Fetalis** This group includes the anemias that are secondary to the development of maternal antibodies against the red cells of the fetus They in clude such syndromes as erythroblastosis fetalis, icterus gravis neonatorum and hy drops fetalis This incompatibility may be based on the Rh factor or major blood groups Sometimes erythroblastosis is simu lated by congenital syphilis

One or more of four causes will explain the presence of acute hemolytic anemia in the newborn infant (1) Rh incompatibility between mother and infant (2) major blood group incompatibility between mother and infant, (3) congenital spherocy tic anemia, and (4) congenitally acquired syphilis For the absolute diagnosis of ery throblastosis fetalis however, specific anti bodies must be demonstrated in the mother s blood against the red cells of the fetus All other evidence, such as Rh or

clinically Another index to the severity of the disease is the reticulocytosis The height of the reticulocytosis bears a rough relationship to the marrow activity Hemolytic anemias, therefore, as a group are usually characterized by increased reticulocytosis elevated pigments of blood destruction in the blood urine and stool depleted numbers of red cells in the peripheral blood if the marrow is unable to produce adequate numbers and often, by demonstrable jaundice It should be pointed out however that patients may have active hemolytic processes without showing all these conditions Thus a slightly jaundiced patient may have a red cell count of 5 000 000 and a hemoglobin of 100 per cent He does not have anemia but only because the marrow is compensating for erythrocyte destruction

Treatment is considered under the separate types of hemolytic anemias

a Congenital Spherocytic Anemia Congenital spherocytic anemia is a syndrome characterized by variable degrees of jaundice spherocytosis of the red cells enlarged spleen reticulocytosis and increased pigment in the blood and urine It may be seen at any age from birth to old age These factors in addition to the family history will establish the diagnosis

Treatment is conservative or by surgery *Conservative treatment* is indicated only in those cases in which for some unrelated reason there is specific contraindication to major surgical intervention for example when there is severe heart disease or active tuberculosis *Splenectomy* should be performed *in all other patients Splenectomy* is recommended because it not only relieves the strain on the marrow in the production of new cells but also prevents acute exacerbations or crises which are hazardous for the patient Furthermore the reduced pigment metabolism lessens the likelihood of pigment stone formation in the gallbladder

After splenectomy blood values are usually restored to normal Although the spherocytes may continue to circulate, they seem to fulfill the function of normal red cells The strain on the marrow is decreased and the reticuloendothelial system is not overloaded with the handling of excess pigment Although it is best to perform the splenectomy during a quiescent phase of the disease occasionally the operation must be performed during periods of acute exacerbation as a life saving measure

The patient and his family should be instructed about the nature of this disease and its transmission *Transfusions* are sometimes perilous Notwithstanding perfect cross matching of blood unexplainable reactions frequently develop Transfusions should be given slowly and discontinued if any ill effects are observed It is best to give transfusions only for specific indications rather than routinely For patients not in crisis transfusions are seldom indicated On the other hand the use of transfusions may be the only way a patient can be prepared for emergency splenectomy

Hormone therapy (see *Acquired Hemolytic Anemia*) may be successfully employed for the abortion of crises or the preparation of patients in exacerbation for surgery

b Acquired Hemolytic Anemia This group includes all varieties of hemolytic anemia of the secondary type In some instances the underlying cause is readily ascertainable where as in others no precipitating cause is found Among the etiologic factors may be mentioned infections (virus pneumonia hemolytic streptococcus *Cl welchii*) drugs (sulfonamides phenylhydrazine) *allergy (favism) neoplasms leukemias* and lymphomas

The treatment of this hemolytic anemia group is unsatisfactory Treatment must be directed to the underlying disease process if it can be disclosed Symptomatic therapy for its control usually involves the use of multiple blood transfusions whenever indicated Careful cross matching of blood must be made and all precautions taken to pre

but the diagnosis depends on the demonstration *of sickle-shaped red corpuscles* There are no specific therapeutic measures effective for the correction of sickle cell anemia The usual hematopoietic agents are entirely *without effect Splenectomy has* been tried but the procedure has been abandoned The extent of treatment depends entirely on the severity of the process During crises transfusions of blood may be needed to correct severe anemia but when the disease is chronic treatment must be symptomatic

f Hemoglobinurias Hemoglobinuria is a manifestation of exceedingly rapid red cell destruction which results in hemoglobinemia and consequently hemoglobinuria It indicates therefore a severe form of hemolytic anemia

Hemoglobinurias stem from a variety of causes Blackwater fever in the course of estivo autumnal malaria * hemoglobinuria following exposure to cold in syphilis an other type known as the *paroxysmal nocturnal* variety develops during the sleeping hours Still another known as *march hemoglobinuria* develops after excessive muscular exercise this however, should be classed as a *myoglobinuria*

The point to be remembered is that the passage of red or black urine when the color is due to hemoglobin is a manifestation of intense red cell destruction

The patient should be treated by blood *transfusions if anemia is severe* In the treatment of the paroxysmal nocturnal hemoglobinurias the transfusions of washed red cells is sometimes followed by less reaction than the use of whole blood If the disease process responsible for it can be uncovered the disease itself should be treated Large amounts of fluid should be given in order to facilitate urinary excretion of the excessive pigments from blood destruction In general the treatment of this entire group is relatively unsatisfactory with the exception of those caused by malaria and syphilis

Transfusions of incompatible blood also result in hemoglobinuria and the same therapeutic measures apply

V Aplastic Anemia

a Idiopathic Aplastic Anemia Aplastic anemia of unknown cause occurs most frequently *in young people but may occur at* any age It is characterized by depleted numbers of all the cellular elements in the blood because of inability of the marrow to produce them The history of the patient should include careful investigation of exposure to infectious or noxious agents

Treatment is unsatisfactory Hematopoietic agents are entirely without value The patient must be supported entirely by blood transfusions in the hope that the marrow will regenerate sufficiently to resume production of its cellular elements Inasmuch as this disease is accompanied also by thrombocytopenia and neutropenia the patient should be observed carefully for evidence of infection which should be prevented if possible Liberal use of penicillin and other antibiotics therefore is recommended for threatened or actual bacterial invasion Splenectomy is of no value *The prognosis is usually poor* Mortality is extremely high No adequate measures have as yet been devised to combat the hemorrhagic tendency consequent to thrombopenia

Osteosclerosis variously refers to so called osteosclerotic anemia osteopetrosis or marble bone disease myelosclerosis and myelophthisic anemia The treatment of these conditions is highly unsatisfactory Again repeated blood transfusions must be depended on to maintain the life of the patient as long as possible Any disease process that may account for the depleted marrow production should be treated as well as possible Such conditions may be coexisting leukemia Hodgkin s disease

* See also Chapter 9

major blood group incompatibility jaundice hepatosplenomegaly, and nucleated red cells in the newborn's blood must be considered inconclusive

Rh incompatibility anemia Anemia of the Rh positive infant which has developed on the basis of Rh incompatibility between mother and infant should be treated with transfusions of Rh negative blood The infant should be fed either breast milk from a source other than the mother or by artificial formula In severe cases it may be necessary to do what is known as an exsanguination transfusion or total blood replacement transfusion No arbitrary figures can be given as to the amount of blood the infant will need The transfusions must be of such frequency and quantity as to maintain the infant s red cell level over 4 5 million at all times Supplemental therapy should include oxygen intravenous glucose together with parenteral vitamins B C and K

Major blood group incompatibility The infant with hemolytic anemia from major blood group incompatibility should be treated with the appropriate blood group after careful studies have been made of both infant and mother with respect to major blood groups and the presence of antibodies in both The principle of treatment is to give the infant a type of blood that will not be subject to destruction by antibodies in the infant s plasma

Anemia caused by syphilis If the hemolytic anemia is caused by syphilis as indicated by bone changes in the infant and positive serologic reaction the disease itself should be treated and transfusions employed for correction of anemia *

Congenital spherocytic anemia In anemia caused by the presence of inherited spherocytic anemia splenectomy should be done as a curative measure

d Mediterranean Anemia Differential diagnosis between sickle cell anemia and Mediterranean anemia may be extremely difficult or even impossible clinically, and may depend entirely on the demonstration or lack of demonstration of sickling Cooley s anemia is the severest form of this disturbance in red cell production and there are many intermediate forms gradually shading from one group to another so that subdivisions are arbitrary and numerous Classically the disease entity is characterized by a familial incidence in people of Mediterranean origin mongoloid facies splenomegaly, typical bone changes evidenced roentgenographically, extreme anemia in early life, and the presence of erythroblasts in the peripheral blood The importance of racial origin in diagnosis has been abandoned as a result of increasing reports of the condition among racial groups far removed from the Mediterranean area

There is no specific treatment for this group of diseases It is noteworthy that even when there is an apparent iron deficiency of the red cells iron therapy is without value This is because the defect lies in an inherent inability to synthesize hemoglobin Splenectomy has been unsuccessfully attempted Except in such instances in which, because of the huge size of the spleen there is mechanical embarrassment, or in instances of splenic hyperfunction with secondary hematologic changes splenectomy is not recommended Cobalt has been used therapeutically but its long term toxic effects are still unknown

e Sickle Cell Anemia Sickle cell anemia is frequently encountered in the course of examination for other ailments The blood studies of Negro patients also reveal sickling without anemia Such patients carry the sickle cell trait. This is almost exclusively a disease observed in Negroes or persons with an admixture of Negro blood In addition to the clinical symptoms of anemia there are rheumatoid manifestations, leg ulcers and acute attacks of pain

* See Chapter 39

VII Refractory Anemias

As the name implies, these are types of anemia that are refractory to treatment They include for the most part those types in which the marrow has been injured to the extent that it is no longer able to produce the required number of red cells In general, they are classified into three groups (1) idiopathic type of aplastic anemia, (2) aplastic or hypoplastic anemia secondary to some noxious agent, the nature of which can be either demonstrated or surmised (3) those caused by general encroachment upon the marrow either by thickened cortical layers of bone, known as osteosclerosis or by widespread metastatic invasion of the marrow from tumors

The disease characteristically is diagnosed by the concomitant presence of anemia leukopenia and thrombocytopenia

Treatment is ineffectual from the point of view of cure or control but life may be prolonged by the removal of the influencing cause when this is possible, by rest and diet, by blood transfusions and the control of hemorrhage, and by the *trial use of BAL*

SUMMARY

A summary of the treatment of all types of anemia crystallizes certain well defined principles

1 Anemia designated as simple chronic anemia associated with such conditions as infectious diseases malnutrition and loss of blood can best be treated by treating the disease causing it

2 Pernicious anemia is treated best by the administration of the hematopoietic principle in the form of *injectable preparations of liver extract* This, for the moment, still remains the treatment of choice

3 Macrocytic anemias, other than pernicious anemia or those characterized by megaloblastic marrow, can probably best be treated by the administration of folic acid by mouth in doses of 10–15 mg per day This includes the macrocytic anemias of sprue pellagra pregnancy, tropical macrocytic anemia, and perhaps others

4 A large group of macrocytic anemias are unresponsive to treatment and are termed *refractory* These include a large percentage of those types resulting from far advanced liver disease and so-called achrestic anemia

5 Liver extract in general is relatively ineffective when given by mouth and should be injected On the other hand there is rare justification for using iron by injection

6 Splenectomy is always the treatment of choice for congenital (spherocytic) hemolytic anemia Other types of hemolytic anemia are, in general, unpredictable in their *response to specific measures of treatment* Hematopoietic agents as such have no value in the treatment of any type of hemolytic anemia

7 All transfusions to infants with erythroblastosis fetalis to all Rh negative females and to all Rh negative males who receive successive transfusions should be only with Rh negative blood

8 Blood transfusions remain the bulwark of treatment in all types of refractory anemia In those in which etiologic agents can be demonstrated removal of the cause is the most important therapeutic measure

lymphosarcoma metastatic carcinomatosis miliary tuberculosis, and perhaps the various primary xanthomatoses

b Secondary Aplastic Anemia Inability of the marrow to produce red cells may be caused by exposure to or ingestion of benzol, excessive amounts of radiation, arsphenamine or other organic arsenical compounds in the treatment of syphilis, gold compounds in the treatment of arthritis sulfonamide drugs chloramphenicol, dinitrophenol trinitrotoluene and a number of other chemical agents BAL (British Anti Lewisite 2 3 dimercaptopropanol) became effectively used first in the treatment of arsenical reactions occurring in the course of antisyphilitic therapy, then in counteracting reactions due to mercury, zinc and copper There have been reports of successful therapy of hematologic as well as dermatologic manifestations It is believed that adequate therapeutic trial of the drug is warranted in any case in which the aplastic anemia is due to heavy metals

Certain hair dyes and many of the anti epileptic drugs such as trimethadione have been reported as causing this disease either on the basis of a toxic depression with actual marrow destruction or through hypersensitivity Mustard gas is known to injure the marrow severely and aplastic anemia may be produced by the administration of certain modern therapeutic agents including nitrogen mustard aminopterin and other folic acid antagonists as well as triethylenemelamine

Whenever the syndrome develops from a demonstrated exposure to any of these agents the predominating therapeutic measure is to remove these agents and treat with repeated whole blood transfusions as indicated If signs of actual or impending infection develop the use of antibiotics is indicated The prognosis in this group is considerably better than that in the so-called idiopathic type

VI Anemias of Pregnancy

All anemias of pregnancy can be classified into four groups physiologic anemia, the microcytic hypochromic type, the macrocytic type, and others of incidental association owing to diseases unrelated to or complicating the pregnancy It is not unusual for physiologic anemia to develop in the third trimester because of hydremia The management of anemias of pregnancy involves both prevention and treatment In order to maintain normal blood values during gestation, the patient should consume at least 50 Gm of animal protein daily, which can be achieved by including in the diet a minimum of one quart of milk, one or two servings of lean meat and one egg daily In nearly all instances anemia can be averted in this way The physiologic anemia characterized by a parallel fall in red blood cells hemoglobin, and hematocrit requires no treatment and responds to none Values as low as 3 5 million erythrocytes 10 Gm (65 per cent) hemoglobin, and 33 per cent hematocrit may be encountered, with no pathologic significance

If hypochromic anemia develops iron is the treatment of choice If the patient develops severe macrocytic anemia (pernicious anemia of pregnancy) it is best to employ transfusions in order to maintain blood values close to normal The patient should also receive crude liver extract in doses of 2–3 cc, or folic acid in 15 mg doses for a week or ten days and then twice weekly during the remainder of the pregnancy As in any other type of severe macrocytic anemia anemia must be treated vigorously until blood values are corrected and then followed by a regimen of maintenance therapy

Cases of macrocytic anemia of pregnancy have been reported in which there was no response to intensive therapy with either liver extract or vitamin B_{12} but there was response to administration of folic acid by mouth

150 r to a total of 500–600 r in each series of treatments The following technic is described by Forkner as being satisfactory for most cases of chronic leukemia 100–150 Kv, 3–10 (ma) at a distance of 25–50 cm with 0 5 mm copper plus 2 mm aluminum filters the radiation being directed to fields 10 × 10 cm to 20 × 20 cm in size From one to three fields can be treated at one time as in chronic myelogenous leukemia radiation being directed over the spleen anteriorly, posteriorly and laterally

After a series of such treatments the patient must be carefully observed leukocyte counts being made at weekly intervals Additional irradiation may not be required for many months As a result of treatment the leukocyte count may fall to nearly normal and occasionally below normal This is not a cause for alarm Radiation therapy may even be safely employed in aleukemic patients when the leukocyte count is subnormal in the beginning

A rising leukocyte count enlargement of the spleen and other evidence of progressive disease in the patient is indication for further treatment and the series may be repeated larger doses being used if necessary Many agents have been suggested to prevent irradiation sickness but most of them have been abandoned after a period of trial Inasmuch as the dosage ordinarily employed in chronic leukemia is relatively small irradiation sickness is seldom encountered

Irradiation should not be used in acute leukemia at any time It can be used in all types of chronic leukemia including the myelocytic lymphocytic and monocytic forms As time goes on the intervals between treatment become shorter and eventually the condition will become refractory with early termination of life likely

A second form of radiation available to those who have the training and facilities is radioactive phosphorus This radioactive isotope P_{32} has a half life of about fourteen and one half days It is given either by mouth or by injection and localizes in the marrow where the radiation is directed against the blood forming tissue It is generally conceded to be as effective as roentgen radiation in the myelocytic type but it has less value in the lymphocytic and monocytic forms For those patients with a high leukocyte count Wintrobe recommends the administration of 0 5–1 millicurie at weekly intervals until the white cell level has dropped to about 30 000 cells per cubic millimeter Further administration is guided by the progress of the patient. This substance is not of value in acute leukemias Radioactive phosphorus produces about the same results in leukemia as does roentgen radiation

Chemical Agents Chemical agents that have been used in the treatment of chronic leukemia include arsenic in the form of Fowler's solution benzene urethane nitrogen mustard and triethylenemelamine Piney believes that arsenic should be used prior to irradiation in doses of five drops of Fowler's solution daily and gradually increased by one drop daily to a maximum of fifteen drops

Benzene was used many years ago and Piney is of the opinion that it deserves a wider use today He recommends 0 5 Gm of benzene mixed with olive oil four times daily given orally in capsules this being increased to eight or ten such doses daily until the leukocytes have fallen to about 50 000 cells per cubic millimeter

Urethane (ethyl carbamate) is an effective chemical agent In approximately 50 to 75 per cent of patients with chronic myelocytic leukemia and 25 to 50 per cent of patients with chronic lymphocytic leukemia satisfactory and sometimes fairly long lasting remissions can be induced Urethane is administered in doses of 1 Gm three times daily until satisfactory hematologic and clinical objectives are achieved In patients responding satisfactorily to urethane irrad

Leukemia

DEFINITION

Leukemia is a disease of unknown etiology which appears suddenly in the acute form, insidiously in the chronic form. It follows a progressive course that is individually variable but always fatal, with the patient sometimes in the beginning of chronic leukemia appearing in good health with the disclosure made accidentally. Clinically the disease is characterized by loss of weight, pallor, increasing exhaustion, symptoms of anemia and of increased metabolic rate, and evidences of bleeding tendency. There may be pressure symptoms from an enlarged spleen and lymph nodes.

Leukemia is fundamentally a disease of the blood forming organs so that the hemopoietic cells fail to behave normally in their growth and differentiation. The result is a proliferation of various blood cells and their entrance into the circulating blood frequently in large numbers.

The acute and chronic forms of leukemia are distinguishable primarily by their duration and the degree of immaturity of the predominating cells, the acute form having the more rapid course with its cells being the more immature. The predominating types of cells offer convenient terms of reference; thus *chronic leukemia* may be subdivided into myelocytic, lymphocytic, and monocytic (reticuloendotheliosis) forms, and *acute leukemia* into myeloblastic, lymphoblastic, and monoblastic forms.

The most convenient classification is as follows:

I. Chronic Leukemias
  a. Myelocytic
  b. Lymphocytic
  c. Monocytic (Reticuloendothelious)
II. Acute Leukemias
  a. Myeloblastic
  b. Lymphoblastic
  c. Monoblastic
III. Multiple Myeloma
IV. Hodgkin's Disease
V. Lymphosarcoma

TREATMENT

General Principles

The rule in the treatment of leukemia lies in the recognition that *the diagnosis of leukemia is not enough to indicate treatment*. This is especially true of chronic leukemias, for which treatment is entirely different from that of acute leukemia. It is therefore important that differential diagnosis be accurate. Indications for treatment of leukemia in order of importance are the presence of (1) anemia, (2) mechanical embarrassment of circulation, of breathing, or of food ingestion because of the massiveness of lymph node or splenic enlargement, and (3) bone pain. *A high white blood cell count is never of itself an indication for treatment of leukemia.*

I. Chronic Leukemia

The treatment of chronic leukemia of all types—myelocytic, lymphocytic, or monocytic—may be conveniently grouped under radiation, chemical agents, and supportive measures.

Radiation. Radiation may be administered by roentgen rays, by radium, and by radioactive isotopes. The use of roentgen rays is the most satisfactory. Radiation may be applied either on a regional basis to enlarged spleen or lymph nodes, or by generalized spray radiation. Most workers prefer the regional type of radiation. The technics vary. If the patient is not acutely ill, radiation is usually directed to the enlarged spleen or lymph nodes for several days with the dosage ranging from 50 to

and ulcers in the soft tissues of the mouth and throughout the intestinal tract Several other folic acid antagonists have been employed for the treatment of acute leukemia but, in general they show no superiority to *aminopterin*

Cortisone and corticotropin (ACTH) have occasionally produced dramatic temporary improvement It is best to give corticotropin in dosages of 25 units every six hours for five days, then 25 units every twelve hours for two days, this supplemented by 100 mg cortisone At the end of this period the corticotropin is discontinued and the cortisone gradually reduced to maintenance dosages which vary from *25 mg to 100 mg Salt restriction and sup*plementation with potassium chloride is advisable throughout this period

Supportive measures include the use of blood transfusions to maintain red cell values and antibiotics to combat secondary infections because the absence of normal granulocytes makes these patients particularly susceptible The hematopoietic agents are entirely without beneficial effect and folic acid is actually harmful Little or nothing can be done for the severe thrombocytopenia and hemorrhages that frequently accompany the disease

For acute myeloblastic and monoblastic *leukemias only the supportive measures* are of any value

III Multiple Myeloma

Ulrich has classified multiple myeloma as (1) solitary benign tumors either osseous or extra-osseous (2) single or multiple malignant tumors of bones with or without extra osseous growth (3) diffuse myelomatosis of the marrow with or without infiltration of other organs and (4) ' plasmacytic leukemia Apitz s classification is essentially the same The tumors comprising the first two groups are relatively common those of the last are not rare The third group diffuse myelomatosis is uncommon

The etiology is unknown Pain tumors deformity, *pathologic fractures and neuro*logic disturbances are the commonest clinical symptoms with symptoms of anemia or abnormal bleeding or suggestions of nephritis frequent Hyperproteinemia is likewise regarded as a criterion of diagnosis together with two or more of the other signs The prognosis has been uniformly unfavorable

At this time it appears that urethane (ethyl carbamate) is the treatment of choice in multiple myeloma Loge and Rundles have reported striking benefit in patients treated with the drug Subsidence of fever and alleviation of bone pain and acute *symptoms were among the salutary effects* There was no progression of destructive bone lesions The number of myeloma cells decreased in the marrow, although serum protein changes were less pronounced

The drug is given in daily dosage of 3-6 Gm by mouth with reduction in the amount of drug if the patient shows an undue amount of nausea or drowsiness Enteric coated tablets of urethane are tolerated best Transfusions should be employed as a supportive measure

Roentgen therapy is occasionally useful for the relief of localized pain It is also used in the treatment of solitary myelomas *after surgical curettage*

IV Hodgkin's Disease

In general Hodgkin s disease has been *classified by Jackson into three* large groups (1) Hodgkin s paragranuloma which is a relatively benign process and with which the patient may live for many years (2) Hodgkin s granuloma *which is* the usual type of reference its infectious or neoplastic nature is in dispute and (3) Hodgkin s sarcoma which has the characteristics of a malignant tumor

The treatment of Hodgkin s disease as the treatment of all other hematologic diseases should be highly individualized Spe-

sation can be deferred until a much later date than would otherwise have been possible Occasionally the two agents can be used together

The use of nitrogen mustard (HN_2) is disappointing in the treatment of chronic leukemias More recently triethylenemelamine (TEM) has been introduced for the treatment of chronic leukemias as well as other diseases In chronic myelocytic leukemia it occasionally produces dramatic short time results whereas in chronic lymphocytic leukemia the drug shows considerable promise but its margin of safety in this condition is extremely narrow

Supportive Measures Supportive measures in the treatment of leukemia include careful attention to oral hygiene to prevent infection by organisms found in the mouth the avoidance of tooth extractions unless safeguarded by antibiotics the treatment of minor infections and the use of multiple blood transfusions whenever anemia is severe or platelets are sufficiently low to produce hemorrhagic manifestations

Rest in bed is indicated only until there has been a remission of fever otherwise patients may be as active as their individual capacities permit

The vitamin requirements should be met by an adequate diet, and supplementation by vitamins is ordinarily not indicated The use of folic acid is definitely contraindicated

Prognosis. As a rule patients with chronic myelocytic leukemia have a life expectancy of about three years those with chronic lymphocytic leukemia considerably longer some patients living ten years and more

II Acute Leukemia A Myeloblastic; B Lymphoblastic C. Monocytic

Accurate differentiation between acute and chronic leukemia is essential because treatment is radically dissimilar and the patient with chronic leukemia does have a better prognosis In acute leukemia death comes quickly after a sudden short grave illness marked by signs of extensive hemorrhagic disorders often initially seen as copious bleeding from mucous membranes with severe anemia fever and prostration toxemia oral necrosis leukemic infiltrations and lymph node and spleen enlargements

In *acute myeloblastic leukemia* it is the severe anemia and thrombocytopenia which underscore the nature of the leukemia—together with the myeloblastic predomination in the marrow

In *acute lymphoblastic leukemia* lymphoblasts may comprise from 50 to 90 per cent of the total cells which are, however, often indistinguishable from myeloblasts In *monoblastic leukemia*, monoblasts predominate There are many criteria required for cellular differentiation of the forms of acute leukemias but these are not of especial interest here

Among specific agents recently advocated for the control of acute lymphocytic leukemia the outstanding one is 4 aminopteroyl glutamic acid better known as aminopterin

Following the work of Farber and his associates, this folic acid antagonist has been used to treat hundreds of cases of acute lymphoblastic leukemia The consensus is that it is effective in prolonging life in perhaps 50 per cent of patients with the disease but seems relatively ineffective in others In a few there is dramatic improvement with restoration of normal peripheral cell values, and in some even a resumption of an almost normal marrow pattern A few patients are alive after three years of aminopterin therapy The drug is usually given in dosages varying from 0 25 mg to 1 mg daily by mouth. Therapy is continued for several days to several weeks and discontinued on resumption of normal blood and marrow observations or the development of toxic lesions. The toxic lesions consist of white well-demarcated mucous like patches

Hemorrhagic Diseases

I Hypoprothrombinemia
  a *Infants*
  b *Adults*
II Hemophilia
  Hereditary Pseudohemophilia
III Thrombocytopenic Purpura
IV Capillary Fragility
V Hyperheparinemia

TREATMENT

I Hypoprothrombinemia

Hypoprothrombinemia may be found in *cases of hemorrhagic disease of the new born* in most cases of obstructive jaundice in which bile is not reaching the intestinal tract in patients with biliary fistulas, with severe liver impairment as in far advanced *cirrhosis and toxic hepatitis* and in cases of intestinal dysfunction such as sprue polyposis ulcerative colitis intestinal fis tulae, and gastrocolic fistulae It is also pro duced by the administration of ' dicumarol as a therapeutic measure as well as of large doses of salicylates Rarely it is present as a familial defect

The treatments of all these conditions *have one objective in common restoration* of the prothrombin level to as nearly nor mal as possible

Infants In treatment of hemorrhagic disease of the newborn, it should be remem bered that only a small percentage of bleed ing in infants occurs because of lowered prothrombin and that *other diseases may* also produce bleeding The treatment con sists of the intramuscular injection of 2 mg of menadione (2 methyl 1 4 naphthoquin one) in oil Kugelmass recommends that 3 mg of hykinone be given intramuscu larly immediately after birth It is advis able to supplement this treatment *with a* transfusion of 35–50 cc of whole blood *Prompt cessation* of bleeding usually fol lows these measures

Adults In the treatment of adult pa tients who have hypoprothrombinemia from any of the causes enumerated it is desirable, as has been said to bring the prothrombin level to as nearly normal as possible, and if it can be brought up to 60 per cent of normal in most cases that is *clinically satisfactory This can be done by* the administration of 2 mg of *menadione* three times daily by mouth or the same result can be obtained by the injection of *2 mg of menadione in corn oil intramuscu* larly two or three times a day until the blood prothrombin reaches a normal level *The* water soluble preparation 4 amino-2 methyl 1 naphthol hydrochloride (*synka min*) may be given intravenously in doses of 2 mg to 5 mg For those patients having hypoprothrombinemia due to inability of the liver to convert vitamin K into pro thrombin, transfusions of whole blood or fresh plasma are necessary

In general, all patients with hypopro*thrombinemia respond satisfactorily to* the administration of *vitamin K* except those in whom the condition has developed be cause of impaired liver function The so called idiopathic hypoprothrombinemia seems to be refractory to the administration of vitamin K and is best treated by repeated *transfusions of blood*

II Hemophilia

The treatment of hemophilia is preven tive and therapeutic, including first the control of the disease by the regulation of marriage and pregnancy, and secondly the treatment of the disease itself

It is well to explain to the patient the *nature of the disease,* how it is inherited through the female and seen only in the male, and explain thoroughly that the hemophiliac himself can transmit the dis

cific lines of therapy are governed by the type of disease process, its relative acuteness or chronicity, degree of involvement and systemic symptoms, such as fever and anemia

In most cases of Hodgkin's disease, *roentgen ray therapy* is the best treatment Roentgenologists do not all agree as to the precise technics by which irradiation should be employed There is agreement that irradiation should be delivered to the diseased areas Spray irradiation seems to be relatively ineffective According to Slaughter and Craver the usual method followed in giving roentgen therapy includes the use of 200–250 Kv, irradiation over large rectangular areas 10 × 20 cm or more, 0 5–1 5 mm Cu filter and administration of 100–400 r a treatment with an entire course as high as 1000 r Patients who are extremely ill should receive small doses at first as should those who show severe systemic reactions Following such therapy large lymph node masses will rapidly regress in size and even masses some distance from the irradiated area may respond favorably Treatments should be repeated whenever there is recurrence of lymph node enlargement fever, anemia or other evidence of exacerbation

Nitrogen mustard is also valuable in the treatment of Hodgkin's disease particularly in patients with fever weakness anemia and signs of toxicity Nitrogen mustard does not cure the disease but it does aid in producing clinical remissions

The usual plan of treatment is the intravenous injection of 0 1 mg of nitrogen mustard per kg body weight daily for a period of four or five days Care must be taken in the injection of the material because if it escapes into surrounding tissue it produces extensive areas of erythema induration and fibrosis It has to be given rapidly as the material decomposes in solution To prevent venous thrombosis it is best to dilute the material or inject it into the tubing of a saline solution infusion previously started Reactions from the injections are sometimes severe, with most patients developing nausea and vomiting Massive sedation is the therapy of choice for this complication

Nitrogen mustard produces clinical improvement in about 80 per cent of the patients when first used The most striking effect is detoxication with fall of fever, and increasing strength, appetite, and weight The size of the lymph nodes may decrease from a single course of treatment, remission may last for weeks to perhaps a year with an average of about six weeks At the end of that time, another similar course can be given Just as with irradiation, however, patients finally become resistant to the action of the drug There is no evidence that it prolongs life Marrow depression and aplasia may follow its administration The temporary severe leukopenia lasts about three weeks and usually requires no treatment

Generalized therapy of Hodkgin's disease is supportive and palliative, including the use of blood transfusions whenever indicated and the use of analgesics or narcotic agents for the relief of pain

Corticotropin (ACTH) and *cortisone* occasionally find usefulness in the treatment of Hodgkin's disease, though their use is usually reserved for such time when the other therapeutic agents are no longer useful Their administration follows a pattern similar to that outlined under acute leukemias

V Lymphosarcoma

From the therapeutic standpoint lymphosarcoma and Hodgkin's disease behave similarly and the methods of therapy discussed under the latter heading apply to the former as well

by tumors such as multiple myeloma or metastatic malignancies The platelets may be reduced because of injury to the marrow by drugs *such as organic arsenicals gold* preparations benzene sulfonamide drugs and perhaps others The platelets may also be depleted because of overactivity of the spleen and hypersensitivity to quinidine sedormid and other drugs or to foods

Thrombocytopenic purpura is generally divided into idiopathic or primary and symptomatic or secondary subgroups

The pathogenesis of primary thrombo*cytopenic purpura is almost as obscure* today as when the disease was first recognized as an entity It has been suggested that a significant correlation exists between the number of eosinophils in the marrow and the clinical course of the patient

Leukopenia is an almost constant finding in secondary *splenogenic thrombocytopenic purpura* The presence of a palpably enlarged spleen in thrombocytopenic purpura virtually rules out the primary and allergic types

Thrombocytopenia of the secondary group is the result of either marrow replacement (by leukemia lymphosarcoma reticuloendothelial or carcinoma cells or fat fibrous tissue or bone) or, to the hypersplenic activity of a diseased spleen Anemia leukopenia or the two may be concomitantly present Regardless of the mech*anism it is important* for diagnostic, prognostic and therapeutic purposes to recognize that secondary splenogenic thrombocytopenia may be due not to marrow replacement but rather to splenic mediation and that relief of thrombocytopenia follows removal of the spleen even though it seems only incidentally involved by a generalized disease process

In the treatment of thrombocytopenic purpura *it is necessary therefore to try* to ascertain the exact cause of thrombocytopenia If the condition is present in association with another disease proper treatment should be directed against that disease If it is caused by administration of *drugs the drugs* must be removed from the therapeutic regimen of the patient In the event that no such diseases or drug administration appear to be accountable for the presence of thrombocytopenia then it must be presumed to exist on the basis of functional overactivity *of the spleen In that* case treatment may be either conservative or by splenectomy Conservative treatment consists of bed rest and the use of *multiple transfusions which is usually fol*lowed by a return to a state of remission In some cases the most satisfactory treatment is splenectomy The platelets promptly rise and the patient ordinarily remains free of the disease thereafter During the operative procedure careful search should be made for accessory spleens which should likewise be removed

Allergic purpuras and perhaps others due to immune mechanisms may respond to the administration of either corticotropin (ACTH) or cortisone The effect of these drugs may be permanent or transient In severe cases employment of the drugs may aid in the preparation of the patient for splenectomy The drugs also find use in the treatment of secondary splenogenic thrombocytopenias especially when these are due to lymphomas or Hodgkin s disease

IV Capillary Fragility

Increased capillary fragility or injury to capillary walls occurs in a number of infectious diseases including typhus fever meningitis various septicemias typhoid fever, scarlet fever, and perhaps many others It is also caused by toxins drug and food sensitivities and deficiency of vitamin C If it is caused by disease the disease itself *is treated* If it is due to sensitivity to some substance careful study should be made to determine the agent to which the patient is

ease to his progeny This usually brings up such questions as advisability of marriage contraceptive measures and sterilization procedures, with ultimate decisions being governed by such factors as severity of the disease and religious beliefs The physician should use every means possible to prevent the perpetuation of this crippling disease that brings unhappiness and tragedy to the victim and his family

The history of repeated bleeding and familial occurrence along with measurement of the coagulation time and prothrombin consumption are necessary to establish the diagnosis if this has not already been established when the patient presents himself for there are several clinical conditions that simulate this grave disorder deep hematoma may be mistaken for a suppurative condition bleeding into a joint may suggest a sarcoma involvement of large joints may simulate arthritis Perthe's disease or syphilis Sometimes kidney tumor pulmonary disease and peptic ulcer are erroneously suggested

There is no satisfactory treatment for hemophilia The best to be hoped for is control of the disease to enable the patient to live a comfortable life as long as possible Many patients die in childhood

Despite the many agents that have been proposed for the treatment of hemophilia such as ovarian extracts placental extract and oxalic acid there is no specific agent that will influence the course of the disease During the periods when blood coagulation is prolonged the best method of controlling the condition by shortening the coagulation time is the utilization of multiple transfusions of fresh whole blood or fresh plasma Although Fraction I of plasma is known to contain an antihemophilic substance this material in concentrated form is generally unavailable and the same substance can be provided by transfusions of fresh plasma It may be necessary to give one or two transfusions each day during periods of active bleeding and sometimes it may have to be done for weeks or months

The local treatment of bleeding wounds can be carried out by the use of pressure bandages, and if the bleeding surface is exposed such bandages may be saturated with fresh blood plasma or thromboplastin solution that is commercially available Usual surgical methods for the control of bleeding should be employed When bleeding occurs in joints internal structures or from the kidneys it can be controlled only by shortening the coagulation time with whole blood or plasma Fresh blood or plasma not over a day old, seems to be superior to the stored material

Joint pains frequently have to be controlled by narcotics and many hemophiliacs become addicted to these drugs Although operative surgery is hazardous it may be necessary and the patient should be prepared for this through decreasing the coagulation time with blood and plasma In such necessary minor surgical procedures as extraction of a tooth the patient should be reinforced with from 100–150 cc of plasma prior to the extraction Postoperative transfusion may be necessary Teeth are sometimes extracted by placing rubber bands around their bases and pushing these farther and farther down daily until the tooth is loosened and removed from its socket.

Hereditary Pseudohemophilia

Treatment for the syndrome generally known as hereditary pseudohemophilia, which occurs in both sexes and may be transmitted by either parent is in general similar to treatment for hemophilia

III Thrombocytopenic Purpura

Thrombocytopenia may develop in association with blood diseases such as leukemia and aplastic anemia in infections, such as meningitis, septicemias typhus fever and subacute bacterial endocarditis and in conditions in which the marrow is invaded

The coexistence of leukemia and polycythemia vera have been so frequently reported as to preclude the possibility of coincidence It appears that patients with polycythemia vera who develop leukemia do so as a consequence of previous irradiation which may actually produce leukemia —aided perhaps by the labile hyperactive hemopoietic apparatus which characterizes polycythemia vera Leukemia develops as a terminal complication of polycythemia vera in approximately 2 per cent of the cases Only one unequivocal case of polycythemia vera was found in the literature in which leukemia developed without previous radiation therapy Neither roentgen nor radioactive phosphorous therapy therefore can be recommended without hesitation until they have been adequately re evaluated in the treatment of polycythemia vera

Venesections

The use of venesections combined with a diet low in iron (less than 6 mg per day) is a simple and satisfactory method of treatment The patient must be bled often enough to keep the hematocrit below 50 per cent At the beginning of treatment, 500 cc of blood can be removed two or three times weekly until the hematocrit reading is nearly normal The amount of blood to be removed thereafter varies in different patients depending for the most part on the faithfulness with which the diet is followed Some require bleedings at intervals of weeks, others at intervals of months

Because the administration of radioactive phosphorus may be followed by a metamorphosis of the polycythemia into leukemia it is well to reserve its use for the debilitated who are intolerant of venesections, patients who have had some form of thrombo-embolic episodes and patients who are unable or unwilling to cooperate with the program of venesections and diet or therapy

Miscellaneous Hematologic Conditions

I INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is a relatively benign and fairly common disease which does not usually require any specific therapy Because it is self limited therapy consists only of palliative symptomatic and supportive measures This includes bed rest during the febrile period restriction of activity, particularly if the spleen is unduly enlarged or if there is a complicative hepatitis the use of antipyretic agents among which acetylsalicylic acid usually is all that is necessary The use of antibiotics is indicated when the angina is complicated by secondary infection

Recently aureomycin has been used in the treatment of infectious mononucleosis based on the presumption that the disease is caused by a virus Its efficacy is negligible

In severe cases pooled serum or plasma might be used but the possibility of thereby producing infectious hepatitis must be weighed against the possible beneficial effects

II AGRANULOCYTOSIS

Agranulocytosis is no longer seen as frequently as formerly when amidopyrine was in common use It is necessary to try to ascertain the cause, and if possible to remove it This requires a careful history to determine prior ingestion of drugs which might produce the disease for example amidopyrine and related compounds the sulfona

sensitive If capillary fragility is caused by a deficiency of vitamin C, it can be treated satisfactorily by the administration of vitamin C (300 mg daily by mouth) and a diet that is high in citrus fruits

Several agents have been employed in the treatment of this and other types of purpura snake venom antivenin rutin, and calcium but none of these agents appears to be effective in the clinical control of the purpuric disorders Recently the use of rutin intravenously in doses of 25 mg daily to weekly, has given encouraging results

V Hyperheparinemia

Occasionally a patient is seen in whom the basic defect appears to be an excess of a circulating heparin like substance Allen and his associates have presented evidence that it can be corrected by the intravenous administration of the dye toluidine blue or protamine sulfate Confirmation of this work by other clinics must be awaited.

Polycythemia Vera

THE diagnosis of polycythemia vera must be positive before its treatment is attempted A large increase in red cell and hemoglobin values usually an enlarged spleen and sometimes variable degrees of hypertension are seen in true polycythemia It is necessary to rule out secondary polycythemia which can develop in the newborn in various cardiac and pulmonary diseases at high altitudes and from chemical agents The presence of such conditions as chronic bronchitis bronchial asthma emphysema and congenital heart disease would suggest secondary polycythemia In their absence a diagnosis of polycythemia vera is justified

The basis for symptoms in these patients is the increased red cell value with a consequently increased viscosity of the blood Therapeutic measures therefore are directed toward keeping in so far as possible the red cell mass within or near normal limits. This can be done by suppressing the output of the red cells from the marrow with such agents as roentgen rays radioactive phosphorus nitrogen mustard triethylenemelamine or by destroying the cells after they have reached the circulatory system with such agents as acetylphenylhydrazine and similar compounds Suppression of the red cells can also be accomplished by removing excessive red cells by repeated venesection

In general the use of acetylphenylhydrazine and other cell destroying agents is not recommended because of the unpredictability of cell destruction and toxic symptoms from liver impairment

Irradiation

Radioactive phosphorus which has a half life of fourteen and a half days and is concentrated in the marrow is an effective form of irradiation It is usually given intravenously in total dosage ranging from 4 to 7 millicuries This is usually adequate for a period of several weeks to many months and a similar dosage can be employed several months later if necessary It is best to perform venesections first to a level of 50 per cent hematocrit, at the same time that the radioactive phosphorus is given since it may take from six to twelve weeks otherwise to see its effect The amount required by patients differs considerably One patient may require only 5 millicuries whereas another may require as much as 2, millicuries before clinical effect is produced

instead Postoperative administration of *heparin and dicumarol* must be *carefully* carried out to prevent the thrombotic closure of the anastomosis

V LIPID DYSTROPHIES

There are three diseases which fall into the classification of disorders of lipid metabolism Gaucher s disease, Niemann Pick s disease, and xanthomatosis or Hand Schuller Christian s syndrome Gaucher s and Niemann Pick s diseases are familial both have a predilection for Jews and both have splenomegaly as their outstanding characteristic The typical lipid filled cells in Gaucher s disease are filled with kerasin while the cells in Niemann Pick s disease reveal a phospholipid *Niemann Pick s disease* has a more rapid progress than Gaucher s with early death within months *Gaucher's disease* is slowly progressive except in infancy when there is neurologic involvement and early death Older patients with Gaucher s disease may live for many years *Treatment is symptomatic* Splenectomy is sometimes attempted in Gaucher s disease when the enlargement of the spleen is oppressive or when symptoms of hypersplenism manifest themselves

Xanthomatosis differs from the other two disorders in that there is no familial incidence and it is bone rather than spleen or liver which is chiefly affected The symptoms depend on the location of the accumulation of abnormal cells Anemia is not always present and is rarely severe It may be unregenerative with leukopenia and slight thrombocytopenia or there may be on occasion pronounced myelophthisic anemia Marrow biopsy gives a characteristic picture

Irradiation has reportedly helped localized lesions but the disease is fatal although *sometimes there is spontaneous remission* with death delayed

mide drugs including even sulfaguanidine, organic arsenical compounds, thiouracil and propylthiouracil tridione, and cinchophen If the patient has been using any of these, their further ingestion should be interdicted

Ideally there should be available to therapy a marrow stimulating agent but until such an agent is forthcoming substitution therapy with fresh blood transfusions must be employed as required An important therapeutic measure is the prevention or treatment of secondary infections that arise because of the absence of granulocytes Penicillin or one of the other antibiotics serves this purpose

In summary intensive penicillin or other antibiotic therapy the use of an occasional blood transfusion and the removal of the offending drug producing the disease comprise the necessary steps in the treatment of agranulocytosis With the employment of such measures the chances for recovery are infinitely better than they were years ago

III HYPERSPLENISM

Hypersplenism includes a variety of clinical syndromes characterized by functional overactivity of the spleen These syndromes have been given many names including primary splenic neutropenia splenic pancytopenia and idiopathic thrombocytopenia Even congenital hemolytic icterus is an example of hypersplenism

The treatment is splenectomy but the diagnosis should be unequivocally established before splenectomy is considered It must be demonstrated that the patient has a normally functioning marrow capable of producing the requisite number of cells Most patients have varying degrees of splenomegaly Before splenectomy is performed the epinephrin test* may be used to demonstrate that the organ is sequestering increased numbers of cells Regardless of the types of blood cells that are being destroyed by the spleen in excessive numbers the signs and symptoms of peripheral blood cell depletion will disappear after splenectomy has been accomplished

During the preoperative and postoperative periods the patient should be supported with blood transfusions Occasionally the spleen has to be removed as an emergency measure notwithstanding existing low cell values

IV BANTI S SYNDROME

There are probably many causes of Banti s syndrome, including those that produce cirrhosis of the liver There are some forms of this syndrome of unknown origin generally referred to as primary fibrocongestive splenomegaly with cirrhosis of the liver, around which has centered the argument as to the value of splenectomy This question should be decided in each individual case as no general rule will apply to all patients And the cause should be sought as soon as the diagnosis of chronic congestive splenomegaly has been established Splenomegaly may precede anemia Leukopenia is the most constant characteristic of the blood with all the types of cells often showing diminution In cases of long duration with severe cirrhosis of the liver or temporarily following an acute hemorrhage macrocytic anemia may develop

The most dangerous complication is bleeding from gastric and esophageal varices Manifestations of hypersplenism usually complicate the condition

No satisfactory form of therapy has been devised Splenectomy alone will ordinarily cure the manifestations of hypersplenism but hemorrhages almost invariably recur Perhaps the best treatment offered to date is the combined operation of splenectomy with a simultaneous end to-side anastomosis of the splenic and left renal vein Anastomosing the portal vein with the inferior vena cava is occasionally done

* See also Chapter 48

At least two types can be recognized by clinical means If possible, it should be distinguished from simple vasomotor lability, in which there are signs of hyper activity of the sympathetic *nervous system* such as blanching of the skin tachycardia apprehension and hypertension which is *primarily systolic*

Diencephalic Syndrome The dience phalic syndrome was so named because *the cardiovascular abnormalities observed* among these patients resemble the vaso motor responses which follow stimulation *of the diencephalon The condition usually* is found in women who are tense and anxious and often weep without adequate change in mood Situational and emotional stimuli produce somatic expression of widespread autonomic stimulation The most characteristic sign is a diffuse blotchy, red blush with fine beads of perspiration, which appears over the neck and upper thorax It may spread to the shoulders and back Simultaneously the blood pressure rises and tachycardia occurs The hands and feet become cold and moist and peri stalsis may be audible

Examinations of the vasculature show this group to be remarkably free of disease for many years Retinal arteriolar sclerosis and cardiac and renal insufficiency may never occur to any great extent although in their late forties or early fifties these patients *frequently* present early evidences of ar teriolar sclerosis Occasionally a patient from this group enters the malignant phase of essential hypertension

Ancestral Hypertension *Another* type which for want of a better term might be called *ancestral hypertension* includes those descendant from national groups which have contributed richly to the arts and sciences They habitually respond more easily and intensely to *all situational* stimuli and express their feelings out wardly to a greater degree than do less sen sitive people

Save for the absence of the blush and *hyperhidrosis the findings and course* of this group are similar to those associated with the diencephalic syndrome Gastro *intestinal hyperactivity is greater and func* tional disease of this system can provide a major problem of diagnosis and treatment. *The arteriolar changes of true* essential hypertension are unusual until the sixth and seventh decades These patients *throughout adult life present multiple and* changing symptoms most of which are due to anxiety or tension states rather than vascular disease

Essential Hypertension

Essential hypertension exists *when the* diastolic blood pressure is almost constantly above 100 mm Hg and when there is evi dence of increased arteriolar *constriction in* the retinal or renal vascular beds Patients with true essential hypertension usually do not reach the age of 60

Malignant Phase

The malignant phase is indicated *by the* appearance of papilledema retinal hemor rhages and exudates proteinuria and microscopic or gross hematuria *Often there* is unexplained loss of weight and malaise The T waves of the electrocardiogram are usually isoelectric or *inverted in leads* I and II The course is rapidly downhill and life expectancy is usually less than two years *but exceptions occur*

Arteriosclerotic Hypertension

Arteriosclerotic hypertension is caused by sclerosis of large elastic blood vessels notably the aorta It is etiologically set *apart from other types* of essential hyper tension and should be carefully differen tiated from them

Patients with this disease develop high blood pressure especially systolic in the early fifties or later The pulse *pressure* is wide and hypertension is inconstant There

15. Hypertension

ROBERT D. TAYLOR
& IRVINE H. PAGE

THE pathogenesis of hypertension and its specific treatment are still unknown. However, it is significant that four disease entities, pheochromocytoma, coarctation of the aorta, unilateral renal disease, and Cushing's syndrome (when caused by an adrenocortical tumor), previously confused with essential hypertension, have now been established as separate diseases. If the adrenal medulla is considered to be a part of the central nervous system, these diseases exemplify isolated abnormalities of each of the four systems—renal, cardiovascular, neural, and endocrine—which are believed to participate in the genesis of essential hypertension.

It would seem possible then that further research will disclose more separable entities within the group now called essential hypertension, and this hope is strengthened by the varying and unpredictable response shown by different patients to the same treatment.

An aspect of this hypothesis, perhaps coincidental, is that it has already become convenient to discuss hypertension under several different headings. The following clinical grouping (Page and Corcoran, 1945) has proved useful in our practice and will be used in the discussion in this chapter.

1. Prehypertension (early or intermittent)
2. Neurogenic
   - A. Diencephalic
   - B. Ancestral
3. Essential
   - A. Adaptation adequate
     - I. With symptoms
     - II. Without symptoms
   - B. Adaptation failing
4. Malignant phase
5. Arteriosclerotic

Prehypertension

Prehypertension occurs almost exclusively among young people in the late teens or early twenties, although it may be found in persons in the fourth or fifth decade of life. The patient rarely is aware that he has any signs of disease until elevated blood pressure is discovered during routine examination. The hypertension usually is slight although it involves both the systolic and diastolic pressures, and is intermittent in character. No measurable vascular abnormalities will be found.

Until a specific antihypertensive drug is available these patients need no treatment and should lead normal lives. Any progress of vascular disease should be evaluated and recorded at yearly intervals.

"Neurogenic" Hypertension

Neurogenic hypertension is probably due to hyperactivity of the sympathetic nervous system and/or the recently described endocrine function of the brain

prognosis and the effects of various treatment can be determined only after repeated and penetrating surveys of the vascular tree This requires an accurate appraisal of all accessible arterioles The frequency and extent of these observations will depend on the rate of tissue deterioration Patients with malignant hypertension may require weekly studies but a prehypertensive patient may need examination only once a year

Emotional guidance must be considered throughout treatment Those who have the diencephalic syndrome experience numerous complaints such as fatigue, giddiness, headache palpitation and dyspnea out of proportion to the severity of the disease They suffer from great anxiety about symptoms and prognosis Constant reassurance and discussion of their problems are necessary Visits to the physician should be even more frequent than for those who have arteriolar disease and may be needed as often as each fortnight Unless this close relation is maintained there may be a pyramiding of fears so that minor symptoms develop into major emotional disturbances

Strokes and heart attacks that cannot be demonstrated objectively are not rare They are apparently emotional crises which cause explosive vasomotor discharges sufficiently severe to mimic cerebral or cardiac accidents The combination of reassurance and liberal use of sedatives is surprisingly effective in keeping these hypertensive patients controlled

Those who have what might be termed ancestral hypertension respond to similar management In addition they are usually overweight and need constant reminding of the dangers that are associated with the combination of obesity and hypertension Frequent office visits are indispensable These patients are in need of a good listener to whom they can offer long descriptions of their symptoms and problems These visits should occur when the patient feels need of them rather than at specified intervals

Exercise also must be considered but there are no fixed rules regarding it A safe practice seems to be to permit any endeavor which affords profit or pleasure but does not produce symptoms or unpleasant fatigue The patient s body response is a more accurate guide to his tolerance than is a physical examination

ANALGESICS AND SEDATIVES

Aspirin or aminopyrine and the long acting barbiturates are used in the treatment of all types of hypertension to control *headache, tension and insomnia* They are invaluable among those patients who present symptoms but little evidence of advancing disease These drugs are fully as useful as any of the wide variety of proprietary combinations offered for patients with hypertension which at best furnish the physician with new drugs or combinations for the sophisticated patient Generally speaking it is safe to use salicylates or aminopyrine in dosages large enough to control headache A gram of either drug four to six times daily may be necessary for some patients The maximum amount which can be given is determined by signs of [illegible]

[illegible] suspected with the appearance of unexplained sore throat

The barbiturates, such as phenobarbital in doses of 16–32 mg four times daily help relieve the anxiety which so often is a part of hypertension and probably reduce the peak rises or fluctuations of arterial pressure Many patients do not continually require such buffers against the stimuli of life therefore it is wise to suggest that the drug be taken only on those days when the need is felt

Where idiosyncrasy to the barbiturates exists chloral hydrate in doses of 0 67–1 0

are signs of sclerosis of the aorta, innominate, subclavian, brachial, and femoral arteries, and retinal vessels Usually kidney function is measurably reduced but not to such a degree that symptoms of dysfunction are produced Both the systolic and diastolic pressures often can be restored to nearly normal levels by bed rest, weight reduction, or sedation

Treatment

GENERAL MEASURES

The mode of life during the treatment of hypertension is important All patients with hypertensive disease will profit from a life of moderation which is as free as possible of emotional, social, and economic conflict Habits, dictated by common sense which supply sensuous and material needs in a limited but enjoyable fashion, should be developed Practical suggestions for attaining such equanimity have already been recorded in the form of a patient's manual (Page, 1943) the seven cardinal principles of which are

1 Avoid indecision
   Do something about soluble problems
   Eschew those beyond solution
2 Do not assume the worries of others
3 Rest thirty minutes twice daily and sleep eight hours each night

[illegible] alk when you can ride, or ride when you can wait
7 Enjoy but do not abuse alcohol, sex smoking and coffee

There are certain aspects of this phase of treatment, however, that can be managed only by the physician Patients have been unduly frightened too often by physicians who, while well meaning exact cooperation through fear Such an approach is rarely justified. Chronic fear is a state which will almost certainly accelerate the course of the disease and, at least, multiply complaints It should be allayed at all costs Often the words of the late President Roosevelt, "The only thing we have to fear is fear itself," can be applied The current wave of lay interest in vascular diseases has produced in most individuals with hypertension a dread of death or invalidism which must be dispelled Progress can be made if patients are taught that hypertension is usually compatible with many years of useful life Furthermore, in addition to the treatments now in use, research gives promise of even more effective methods within the life span remaining for many of us

The necessary cooperation of patients often will be obtained if they appreciate that the disease is chronic and that by giving careful attention to the physician's advice, life may be considerably prolonged The problem of therapy for someone with well-compensated hypertension is not as important for the present as for the future for which he must plan The patient has a right to know that any treatment cannot be guaranteed as a cure and that the most effective regimen for him may be found only by trial and error

Too frequently, patients and physicians assume that a single extensive examination will permit an immediate decision concerning the proper treatment This is not true now, and it is unlikely that it will become true in the immediate future All patients with arterial hypertension have a lifetime problem The course of the disease, the

TABLE 16 IDEAL WEIGHTS FOR MEN AND WOMEN (Age 25 and Over, as Ordinarily Dressed)

MEN

Height with shoes		Weight (lb)		
Feet	Inches	Small Frame	Medium Frame	Large Frame
5	2	116 125	124–133	131–142
5	3	119 128	127–136	133–144
5	4	122 132	130–140	137–149
5	5	126 136	134–144	141–153
5	6	129 139	137–147	145–157
5	7	133 143	141–151	149–162
5	8	136–147	145–156	153–166
5	9	140–151	149–160	157–170
5	10	144–155	153–164	161–175
5	11	148 159	157–168	165–180
6	0	152 164	161–173	169–185
6	1	157–169	166–178	174–190
6	2	163–175	171–184	179–196
6	3	168 180	176–189	184–202

WOMEN

Height with shoes		Weight (lb)		
Feet	Inches	Small Frame	Medium Frame	Large Frame
5	0	105–113	112–120	119–129
5	1	107–115	114–122	121–131
5	2	110–118	117–125	124–135
5	3	113–121	120–128	127–138
5	4	116–125	124 132	131–142
5	5	119–128	127–135	133–145
5	6	123 132	130–140	138–150
5	7	126–136	134–144	142–154
5	8	129–139	137–147	145–158
5	9	133–143	141 151	149–162
5	10	136–147	145–155	152–166
5	11	139–150	148–158	155–169
6	0	141–153	151–163	160–174

From the Metropolitan Life Insurance Co Statistical Bureau June 1943

work by 35 per cent Newburg found that any degree of obesity, after the age of 45 is as serious a threat to longevity as valvular heart disease

Any low caloric diet can produce reduction of body weight provided it is used faithfully Body weight is analogous to one's bank account it grows and shrinks only as one adds and takes away from it

For most people who are active in business or society, it is difficult to follow a quantitative diet We use a simple and practical exclusion diet which is palatable and provides all the necessary food components Five items are excluded from the diet until a normal body weight is attained These are (1) all forms of pastry, (2) bread and butter, (3) potatoes and gravy, (4) oily salad dressings and (5) candies and soft drinks This program permits free use of lean meats, fruits and vegetables cheese milk, custards, gelatins, etc.

If the patient is not able to follow a reducing diet, it may be necessary to supplement his failing willpower with amphetamine sulfate to depress the appetite It can be given in doses of 5 mg and occasionally 10 mg three times daily If cerebral stimulation is unpleasant or interferes with sleep, it can be counteracted by appropriate doses of phenobarbital

Once the desired body weight is established, the restrictions can be modified as long as there is no increase in weight According to Newburg the ideal body weight compatible with the longest life is that present at 25 years of age, provided the patient was not at that time obese Ideal body weights as related to body build and height have been tabulated by the Metropolitan Life Insurance Company (Table 16) *

The association of cardiac and vascular attacks with ingestion of large meals is more than accidental It is explained by the increased cardiac work which digestion induces Hence, patients with actual or potential hypertensive heart disease should always deny themselves the luxury of the gourmand and be content with the less voluminous savor of the gourmet Food should be taken in moderate amounts four to six times daily

Specific dietary programs that have been helpful in the management of some

* See also Chapter 51

Gm four times daily serves admirably as a sedative The unpleasant taste can be partially masked by the use of syrup of orange as a vehicle

THIOCYANATE

Thiocyanate continues to be a useful drug for the control of intractable headache among patients with hypertensive disease It is particularly valuable among those with well adapted essential hypertension or hypertension secondary to arteriosclerosis Barker recommended that the dosage be regulated so that a serum concentration of 8–12 mg per 100 cc be maintained This usually requires about 0 6 to 1 0 Gm daily Such levels are not always necessary Probably the best rule is to use an amount that relieves symptoms In our experience serum concentrations of 2 to 5 mg per 100 cc often suffice

Enteric-coated tablets of thiocyanate which contain 0 067 and 0 2 Gm are available but are not recommended because they may pass through the intestines undissolved furthermore solutions of the drug are as well tolerated and are less expensive The efficiency of the drug seems to be enhanced when given with small amounts of phenobarbital This can be conveniently accomplished with a prescription containing equal parts of elixir of sodium thiocyanate and elixir of phenobarbital Given in doses of 1 teaspoonful three or four times daily to patients in whom urea clearance is more than 50 per cent of the average normal it will produce effective serum concentrations with little danger of toxic levels occurring However in the presence of extensive renal disease extreme caution must be used Blood levels of thiocyanate should be measured at least weekly until an effective daily dosage is established Once this has been attained measurements can be made at intervals of four to six weeks All specimens should be examined in a qualified laboratory No simple bedside test has yet been devised

Untoward reactions to thiocyanate occur in about 12 per cent of patients In our experience these are rarely serious Most commonly the patient complains of some degree of lassitude and weakness while first taking the drug However if the drug is continued for two to four weeks in spite of these complaints there will be a gradual return of well being Possibly 5 per cent of patients will develop a macular type of skin rash accompanied by pruritus As a rule this appears over the legs and arms and fades promptly when the drug is discontinued Enlargement of the thyroid gland with signs of myxedema is noted in about 2 per cent Anorexia diarrhea thrombophlebitis psychotic manifestations and osteoporosis have all been reported as complications of thiocyanate treatment but the incidence is not high Deaths due to the drug have been reported Many of these fatalities occurred among patients who were extremely ill or had advanced renal disease which permitted blood levels to become too high

Signs of toxicity disappear within a few days after the drug is discontinued Recovery may be accelerated by inducing water diuresis and is usually complete within three weeks Thereafter if symptoms can not otherwise be controlled the drug may be readministered after a rest period of four to six weeks as more than half of these people fail to develop unpleasant reactions on a second course of treatment

DIETARY MEASURES

There are a few dietary principles that apply to all persons with vascular diseases and which should be established as lifetime habits. The increased cardiac work which attends obesity should be avoided Masters measured the effect of increased body weight and estimated that an excess of 25 lb of body weight increases cardiac

TABLE 18 LOW-SODIUM DIET

TOTAL DAILY FOOD ALLOWANCE

2 servings fruit (from list)
1 serving of cereal (from list)
5 slices of bread (unsalted)
6 squares of butter (unsalted)
1 quart of salt free milk
1 egg
3 ounces meat (from list)
½ cupful of potato or rice
2 servings vegetable (from list)
2 servings of dessert (from list)
3 tablespoonfuls white sugar

TO THIS MAY BE ADDED

1 slice of bread *or*
2 servings of fresh fruit *or*
2 servings of beverage *or*
2 servings of sweets (from list)

SAMPLE MENU

Breakfast
½ cupful orange juice
1 cupful cooked oatmeal
2 slices salt free bread
2 squares salt free butter
½ cupful liquid salt free milk
black coffee

Luncheon
1 poached egg
½ cupful steamed rice
1½ slices salt free bread
2 squares salt free butter
1 small baked apple
1 cupful liquid salt free milk
1 serving of dessert (from list)

Dinner
3 ounces broiled fresh fish
½ cupful frozen asparagus
1 cupful sliced tomatoes
1½ slices salt free bread
1 serving of dessert (from list)
2 squares salt free butter
½ cupful liquid salt free milk

BETWEEN MEALS ALLOWED ADDITIONS
(1 serving equals ½ cupful)

All fresh fruits (raw and cooked) and fruit juices may be used Canned, dried, or frozen fruits and juices may likewise be used (unless the label states that salt or sodium benzoate has been added)

VEGETABLE LIST
(1 serving equals ½ cupful)

All vegetables in the following list may be used with vinegar, lemon juice, salad oils or any of the permissible seasonings mentioned in list of condiments

Fresh

Asparagus	Beans, green	Beans, lima	Broccoli
Brussels sprouts	Cabbage	Carrots	Cauliflower
Corn	Cowpeas	Cucumber	Eggplant
Endive	Lettuce	Macaroni	Mushrooms
Okra	Onions	Parsley	Parsnips
Peas	Potato	Pumpkin	Radishes
Rice	Soybeans	Spaghetti	Squash (all kinds)
Tomatoes	Turnips (white, yellow)	Turnip leaves	

Frozen

Asparagus	Beans, green	Brussel sprouts	Cauliflower
Corn			

Dried

Beans, navy	Soybeans

TABLE 17 RICE DIET

Approximate composition C 490, P 18, Cal 2032

BREAKFAST	
Fruit juice	2 servings
Steamed or boiled rice	1½ cupsful
Sugar	4 tablespoons
Fruit	3 servings
LUNCHEON AND DINNER	
Baked, steamed or boiled rice	1½ cupsful
Sugar	4 tablespoons
Fruit juice	2 servings
Fruit	2 servings
FRUITS	**AMT IN ONE SERVING**
Apple	½ medium size
Applesauce	6 tablespoons
Apricots	2 medium
Banana	½ small
Blackberries	1½ cupsful
Blueberries	⅔ cupful
Cantaloupe	½ small melon
Cherries (sweet)	½ cupful
Cranberries	1 cupful
Gooseberries	⅔ cupful
Grapes, seedless	40 small
Grapes Tokay	10 average
Honeydew	½ cupful cubed
Lemon juice	¼ cupful
Lime juice	¼ cupful
Orange	1 medium
Orange juice	½ glassful
Pineapple	½ cupful or 2 slices
Pineapple juice	Scant ½ glassful
Peach	1 medium
Pear	2 average
Plums	2 average
Raspberries	⅔ cupful
Strawberries	1½ cupsful
Watermelon	½ slice 1 inch thick

GENERAL INSTRUCTIONS

Avoid nuts, dates, avocadoes, and all dried fruits. Avoid canned fruit or juice to which anything other than sugar is added. Avoid tomato juice or other vegetable juices. *Avoid all salt in cooking and do not add salt* at the table. Rice should be cooked without salt, milk, or fat. Use exactly the kinds and amounts of food listed—no more or less.

patients with essential hypertension with failing adaptation and for occasional malignant hypertensives have but one known factor in common which is rigid restriction of sodium intake. Such diets were first suggested in 1904 and again by Allen in 1922. This approach to the treatment of high blood pressure then was not widely used because the studies were not completely convincing to many observers. In 1930 Kempner suggested the "rice diet" (Table 17) consisting of boiled, unseasoned rice, fresh fruit and fruit juices, and glucose with a total daily caloric value of 2000. This diet is supplemented with vitamins and ferrous sulfate.

Such a program will serve several known needs of patients with vascular disease since its monotony discourages overeating, it will reduce body weight, if there is congestive heart failure sodium depletion is provided, and if azotemia is present, the low protein intake is helpful in its control. As for specific effects on the blood pressure, most evidence suggests that the restriction of sodium to less than 200 mg per day is the means by which this is accomplished. Many patients will not adhere to the rice diet for any length of time.

Until there is evidence to prove that the hypotensive effects of diet are due to factors other than sodium deprivation and caloric restriction, the same results may be accomplished with a more palatable diet that is more adequate in protein. A combination of sodium-free milk protein ("Lonalac") and the usual foods that are sodium poor is acceptable to most patients (Table 18). The difficulty inherent in providing this type of treatment is the omnipresence of sodium. It is difficult and tedious, if not almost impossible, to attain adequate sodium restriction for some ambulatory patients. Unless this is done, the entire effort is useless except for weight reduction. Consequently, the daily output of urinary sodium must be measured at least weekly; errors can thus be sought and corrected. Once a routine is established, and the output of urinary sodium reduced to less than 200 mg per day, measurements are necessary only at intervals of three to six weeks.

In order to increase the palatability of sodium-poor diets, many *salt substitutes*

TABLE 18 LOW SODIUM DIET—*Continued*

SOURCES OF SODIUM TO BE AVOIDED

1 Salt both at the table and in cooking and preparing food
2 Commercially processed foods in which salt has been added These include
 A Smoked salt-cured and other processed meats, such as ham, bacon salt pork sausages corned beef salt fish canned meats and fish bouillon cubes, and meat extracts
 B Cheese
 C Pickled and spiced products such as olives pickles catsup sauces sauerkraut, salad dressings and prepared mustard
 D Canned vegetables and soups
 E Salted butter margarine peanut butter and cheese spreads
 F Celery beets beet greens kale dandelion mustard greens spinach
 G Celery salt onion salt garlic salt meat flavoring prepared horseradish, Worcestershire sauce
 H Ordinary bakery goods and crackers
 I *Prepared cereals other than those on the cereal list*
 J All other salted foods such as pretzels potato chips popcorn salted nuts, most candies and candy bars commercial jellies and jams
3 Soda products such as baking soda and baking powder, self rising flours including pancake biscuit muffin and cake mixes also various laxatives and other remedies containing salts Consult the doctor before taking any medication
4 Beer and wines Consult doctor before using any alcoholic beverage
5 Foods labeled salt free or salt restricted unless checked with dietitian
6 Water which has been run through water softening equipment

have been provided None is perfect However, some patients can learn to enjoy food that is seasoned with potassium chloride or mixtures of ammonium and potassium chloride In general salt substitutes should be free of sodium and lithium The latter substance should be avoided because it has been shown to produce tremor muscle *twitches apathy, difficult mentation,* blurring of vision confusion coma and even death in some patients whose diets are low in sodium

As far as is known it is safe to assume that dietary measures will not be effective if the blood pressure has not fallen after three months of rigid sodium deprivation Should there be reduction of blood pressure the maximum degree probably will be attained after two *to three months At the* end of this time, the diet can be made more liberal as dictated by the effects of deviations from the previous schedule upon the blood pressure

SURGICAL TREATMENT

Coarctation of the aorta, pheochromocytoma and pituitary basophilism (Cushing s syndrome) are types of arterial hypertension which can often be cured by proper operation if an accurate diagnosis is made and if the lesion is specifically located and is operable The decision as to whether these patients can be helped *lies with the* surgeon Unilateral renal disease requires more consideration from the internist. *Frequently,* nephrectomy has no effect upon the blood pressure or the course of vascular disease Nonetheless there are patients in whom disease of a single kidney produces hypertension in a manner similar to that observed in animals with a clamp on the renal artery or with silk induced perinephritis There is no way of *knowing* preoperatively what effect nephrectomy will have upon the blood pressure al*though experience* is helpful in determining what may be anticipated

In rats experiments lasting only a few weeks have shown that removal of the kidney causing the hypertension is followed by a return of blood pressure to normal After the hypertension has persisted for months little change is observed *Similar* conditions seem to prevail in human beings

TABLE 18—Continued

MEAT LIST

(1 serving of meat is 3 ounces. It measures $6 \times 3\frac{3}{4} \times \frac{3}{4}$. Meat may be fried in lard or unsalted vegetable fats or oils.)

Beef (fresh or frozen)	Fish (fresh)
Lamb (fresh or frozen)	Oysters (fresh)
Pork (fresh or frozen)	Chicken (fresh)
Rabbit (fresh or frozen)	Duck
Veal (fresh or frozen)	Turkey
Quail	

CEREAL LIST

(1 serving is 1 cupful cooked or 2 cupfuls prepared.)

Barley, pearled	Corn meal	Cracked wheat	Farina, plain
Instant Ralston	Maltex	Oatmeal (rolled oats)	Pettijohn's
Puffed rice	Puffed wheat	Rice	Shredded wheat
Wheat germ	Wheatena		

BEVERAGE LIST

(1 glassful is 8 ounces)

Apple juice	Coffee	Ginger ale	Grape juice
Grapefruit juice	Lemonade	Orange juice	Orange crush
Pineapple juice	Postum	Prune juice	Tangerine juice
Tea			

Reconstituted salt-free milk, plain or flavored with unsweetened chocolate, vanilla or caramel; fresh pineapple, strawberry, or banana flavoring may be used.

DESSERT LIST

(1 serving is ½ cupful)

Cornstarch puddings	Fruit tapioca puddings
Gelatin desserts made with plain gelatin fruits and juices	Rice with fruit and sugar

SWEET LIST

Honey	*Home canned jams*	*Home canned jellies*	*Home canned marmalades*
Homemade candies	Popcorn with syrup	Hershey's chocolate syrup	

Candies should be made with white sugar and salt-free milk.

CONDIMENTS AND FLAVORING LIST

Allspice	Caraway	Cinnamon	Curry powder
Garlic	Ginger	Lemon extract	Lemon juice
Mace	Mustard powder	Nutmeg	Paprika
Pepper, black	Pepper, red	Pepper, white	Peppermint extract
Sage	Sugar, white	Thyme	Turmeric
Vanilla extract	Vinegar	Walnut extract	Sodium-free salt substitutes

FATS LIST

Crisco	Lard	Spry	Any unsalted pure food oil

MISCELLANEOUS FOODS

Unsalted nuts	Unsalted popcorn

BREAD SUBSTITUTES

Low-sodium caraway seed bread	Low-sodium cinnamon roll
Special passover or thin tea matzoth	

RECIPE FOR SALT FREE BREAD

15 cups flour	2 oz. unsalted shortening
2½ oz. sugar	1 pt. water
1 oz. yeast	

Follow the same method as for ordinary bread. Yield for this recipe is two loaves. Bake in 400° oven for 40 minutes.

PYROGENS

It has been known for many years that mechanisms which elicit leukocytosis and fever cause vasodilatation and reduction of blood pressure in some patients with arterial hypertension. We have shown that prolonged treatment with bacterial products which produce fever is often effective in the control of the malignant phase of essential hypertension. A convenient form of pyrogen is one derived from nonpathogenic bacilli.

Hospitalization during this treatment is necessary. The material (piromen'—Baxter) is administered by single intravenous injections in amounts necessary to cause a daily rise of temperature to 102°–104° F. The initial dose is 0.5 cc. of solution containing 50 μg. of solid material per cc. Dosage is determined by the rise in temperature observed on the previous day. Tolerance of the patient rapidly increases and within two or three weeks 10 to 30 cc. of solution containing 400 μg. per cc. may be needed daily. If these volumes do not induce temperatures of 102°–104° F., it is wise to discontinue injections for two to five days. During this interval tolerance decreases and patient morale is enhanced. Treatment with one half the last dose is then resumed. The period of hospitalization depends upon the patient's response and usually extends from three to six months.

In view of the fatal outcome of this type of hypertension, the time and discomfort of treatment are inconsequential. The daily febrile bouts should be induced as long as the blood pressure continues to fall and other evidences of necrotizing arteriolitis regress. Within three to six weeks the blood pressure should approach normal levels or reach a plateau much lower than the initial values. During this interval retinopathy, cardiac and renal disease will be improved measurably; however, the major changes will occur gradually during the subsequent two to three months. When the blood pressure is normal or fails to fall further, the frequency of injections may be decreased provided arterial pressure does *not rise sharply*. *A gradual increase* almost always is noted regardless of the degree of fever.

This regimen may lead to improvement of hemorrhagic retinopathy, hypertensive heart disease, proteinuria and hematuria. If there has been loss of weight, the weight usually is regained and subjective symptoms are controlled. Treatment should be continued as long as there is any sign of improvement. As indicated, this may require six months of hospitalization. Toward the end of that time, the blood pressure may have returned to hypertensive levels but signs of malignant progression usually do not recur. The problem then becomes similar to that which is presented by essential hypertension.

There are several unpleasant aspects to such a program. The time required and expense are obvious. Unless rigors and fever are inhibited by antipyretics they always follow injections of adequate amounts of pyrogen. The degree of fever is a helpful guide to the amount required and unless it is extremely *distressing*, fever need not be suppressed. However, for emotionally immature patients who tolerate inconveniences poorly, aminopyrine 3 to 6 Gm. daily will usually maintain a normal body temperature with no effects upon the hypotensive component of the treatment. The amount of pyrogen to be given can be estimated for intervals of four to five days. The antipyretic is then withdrawn for forty-eight hours while the pyrogen is continued. This will indicate whether dosage has been effective according to the degree of fever that is induced. Nausea and vomiting occasionally accompany the fever. Sedatives and even small doses of opiates are helpful on such occasions. Some patients complain of intense, intermittent constricting pains in lumbar muscles and in the *precordium*. *These, as a rule,* persist only

Those benefiting from nephrectomy usually are children or patients with a short history of hypertension. The chief indications for nephrectomy in hypertensives are usually those that would lead to operation whether or not hypertension was present.

Exceptions to this rule occur. If the presence of unilateral renal disease can be established in patients giving no family history of hypertensive disease the chances are greater that hypertension is due to an acquired lesion than among those having a familial background. The case for nephrectomy is further strengthened if there is little arteriolar disease which means that the disease probably is of comparatively short duration.

Sympathectomy

Sympathectomy is useful at times. Many types of operation have been devised. These include anterior nerve root section, denervation of and partial resection of the adrenal glands, splanchnic nerve resection, celiac ganglionectomy, lumbodorsal sympathectomy and ganglionectomy, and total sympathectomy and ganglionectomy. No carefully controlled or strictly comparable studies have been made to establish which of these is the most effective. Until such evidence is available, the operation of lumbodorsal sympathectomy and ganglionectomy (Smithwick) is recommended. It permits extensive denervation with minimal mortality and morbidity. It is widely used at present, and until a more physiologic approach to the treatment of hypertension is known, it will remain as the therapy of choice for some patients.

Of all the tests suggested for selection of patients for sympathectomy, none singly or combined, have been successful. Sedation tests, pressor tests, pharmacologic interruption of the sympathetic nervous system by procaine, tetraethylammonium chloride, "Priscol," and "Dibenamine" have given little help. Some patients exhibiting no fall of blood pressure after these procedures receive no benefit from operation, but this does not necessarily mean that the method has been selective.

At present the best indications for operation are (1) evidences of advancing vascular disease, (2) symptoms that are incapacitating and do not respond to dietary or medical treatment, (3) early malignant hypertension, and (4) normal renal function.

These indications have been used by us for the past seventeen years. An example from a large number of patients will serve to illustrate the results which we have obtained. Of 86 patients, 21 had malignant hypertension, 55 essential hypertension and 10 neurogenic hypertension. Ten of the entire group (11.6 per cent) of whom 9 had essential hypertension and 1 malignant, showed almost complete remission of disease. That is, the blood pressure measured in the supine position was usually normal and both objective and subjective signs of disease disappeared. Eighteen (21 per cent) of whom 6 had malignant hypertension, 10 essential and 2 neurogenic, had considerable objective improvement. There was unquestionable reduction of the average blood pressure and measurable regression of retinal and cardiac disease. Subjective symptoms had usually completely disappeared.

Twenty-six (30 per cent) of this group of patients (4 with malignant hypertension, 16 with essential and 6 with "neurogenic") experienced total or partial symptomatic improvement but there were slight or no measurable changes in the degree of vascular disease. The operation had no effect upon the disease of 32 (37 per cent) (10 with malignant hypertension, 20 with essential and 2 with "neurogenic") and 17 of these patients are now dead. There were 2 others who died among these 86 patients

awaited with interest, especially because it may give some clue as to the mechanism of action

RUTIN

Rutin is a flavone similar to hesperidin (vitamin P) which is believed by some to be of aid in the control of capillary fragility However capillary fragility is extremely difficult to measure and further more, there is little knowledge of its significance in disease or the degree to which it varies under normal conditions The value of hesperidin in the control of hemorrhagic tendencies has never been established The evidence which has led to the use of rutin in hypertension is at best not impressive Until more substantial evidence is presented, rutin should not be used in general practice

Complications

HYPERTENSIVE ENCEPHALOPATHY

Volhard was *chiefly responsible for the* recognition of what was formerly believed to be acute uremia as a cerebral manifestation of hypertension Fishberg and Oppenheimer proposed the name 'hypertensive encephalopathy' and added materially to our knowledge of the condition *To them this diagnosis was limited to* sudden onset of convulsions and unconsciousness without permanent signs of neurologic changes Often such episodes are preceded or followed by severe headache or nausea and vomiting The term now has a broader connotation and includes all symptoms referable to the central nervous system that cannot be ascribed to hemorrhage or thrombosis Bouts of mental confusion giddiness or vertigo, waves of nausea, and generalized weakness with hyperhidrosis are forms of encephalopathy Transient paralysis paresthesia, amaurosis and severe headache with vomiting may occur independently or associated with other signs of cerebral insufficiency

Unless such complications are transitory, *hospitalization is necessary* Convulsive *seizures may be controlled* by *sodium amytal* (0 25–0 5 Gm) intravenously Should headache with confusion and vomiting be the major problem, bed rest, adequate sedation, and occasionally morphine sulfate (*11–17 mg every three or four hours*) usually lead to recovery within thirty six to forty eight hours

Lumbar puncture is usually suggested for the treatment of encephalopathy, however, only once have we seen it to be dramatically effective It often accentuates or *prolongs headache It should not* be a routine procedure, but rather a means of detecting intracranial hemorrhage If during the course of such a diagnostic puncture the cerebrospinal fluid pressure is found to be greatly elevated (above 200 mm H_2O) the slow removal of enough fluid to restore the pressure to normal may be helpful

CEREBRAL THROMBOSIS

Cerebral thrombosis which results in *permanent neurologic change but does not* cripple or produce unconsciousness should be viewed with as much optimism as possible Unless the patient is greatly disturbed and anxious he need not be put to bed or hospitalized Sedatives and encouragement may minimize the occasion so that it will not interrupt normal activity Since *it is presumed* that vessels in proximity to the site of thrombus formation exhibit reflex spasm attempts to induce dilatation by sympathetic paralysis *have been* made

a few minutes If they are intolerable and do not decrease promptly intravenous injection of 0 25–0 5 Gm of sodium amytal will cause relaxation and comfort

Treatment with bacterial pyrogens is reserved for those patients with the malignant phase of essential hypertension who have signs of a particularly fulminating process In our limited experience it is possible to control, at least temporarily this phase of hypertension regardless of the severity of retinal and cardiac disease provided the renal tubular excretory capacity is above 50 per cent of normal as measured by the ability to excrete aminohippurate or "diodrast If kidney reserve is more *severely reduced it is still worth treating* the patient since treatments other than sympathectomy have little to offer and an occasional case does surprisingly well in spite of advanced nephrosclerosis

For those patients who have but moderate signs of necrotizing arteriolitis and cannot undertake long hospitalization lumbodorsal sympathectomy is indicated This procedure offers a reasonable chance that the disease will be arrested for a period of two to three years and will permit resumption of normal activity at an earlier date than will treatment with pyrogens

If hospitalization is impossible or should the response to pyrogens be transitory or unsatisfactory sodium depletion may be added to the program

After the malignant phase is arrested sympathectomy or sodium restriction should be considered as they would for any patient with essential hypertension

If the malignant syndrome persists sympathectomy followed by sodium depletion and/or pyrogen is worthy of trial

HYDRAZINOPHTHALAZINE AND METHONIUM IONS

Data are inadequate to permit critical and mature consideration of hydrazinophthalazine and methonium ions separately or in combination, in the prolonged treatment of essential hypertension Hydrazinophthalazine may in part act by inhibiting the endocrine vasopressor mechanism of the midbrain and possibly in part by peripheral vasodilatation It is effective orally and parenterally In dosages ranging from 50 to 200 mg four times daily, it reduces blood pressure significantly in approximately one-half of patients with essential hypertension The eyeground changes in malignant hypertension have been observed to reverse in some patients Much time must elapse before the position of this drug in the prolonged treatment of hypertension is known

There are often unpleasant side reactions *Usually they are transient and can* be controlled with ergotamine benadryl or sedatives and analgesics Ten per cent of patients are unable to take the drug Occasional fever anorexia nausea and vomiting headache esophageal and gastric burning may occur At some time many patients have transient edema of the feet and periorbital tissues No serious or permanent changes have been observed to follow There is a growing suspicion that tolerance to the drug may develop

Methonium ions (chloride or bromide salts of hexamethoniums or pentamethonium) induce prolonged sympathetic blockade by partially inhibiting ganglionic transmission They are effective in relatively small doses (25 250 mg) when given intramuscularly and by mouth in much larger doses (2–6 Gm) Duration of activity is ten to twelve hours however *tolerance* to the drug often appears after three to twelve weeks and in spite of increasing dosages the hypotensive effects are lost. During the period they are effective there is orthostatic hypotension, which may be troublesome

Schroeder finds that the simultaneous oral administration of these two drugs produces a synergistic rather than an additive effect which causes better results than either alone The evidence for this will be

16. Respiratory Diseases

H CORWIN HINSHAW

Pulmonary Tuberculosis

IT IS usually conceded that the solution of the complex problems encountered in the treatment of active pulmonary tuberculosis should be undertaken by specialists Furthermore the prolonged and serious hazard of contagion often necessitates institutional care However the physician engaged in general practice may be called upon to supply interim care to patients who are awaiting admission to a sanatorium or a hospital and even more frequently he must supervise the aftercare of a patient for many months or years after his disease appears to have been arrested The great popularity of mass roentgen ray surveys has led to the discovery of many thousands of patients whose pulmonary tuberculosis is in a stage of uncertain activity and the physician often is called upon to advise such patients on the best way of avoiding the reactivation of latent disease This is preventive medicine in its purest form and frequently involves the exercise of keen judgment and strictest attention to minor details In many instances the family physician is admirably qualified to understand problems of the patient s home life important occupational stresses and environmental hazards which the distant specialist may not comprehend

Symptomless latent tuberculosis may be present in good health or in the presence of other disease Such latent tuberculosis may become reactivated as a result of the stress of intercurrent infection surgery childbearing malnutrition overwork or poor personal hygiene For these reasons roentgen ray examination of the chest has become recognized as an important routine procedure in general practice and in all the medical and surgical specialties

Although the foregoing principles are widely accepted there is less uniformity of thought with regard to the medical or surgical management of active and latent forms of tuberculosis

DIAGNOSTIC CRITERIA

There are three important clinical categories into which all patients with evidence of tuberculosis may be placed There are (1) active tuberculosis (2) inactive or latent tuberculosis and (3) tuberculosis of undetermined activity It is much less important to determine whether the disease be minimal moderately advanced or far advanced Since all patients with active tuberculosis need treatment no consideration of therapy would be complete unless the criteria for determination of activity is discussed in

Procaine infiltration of the stellate ganglion on the side of the area of damage has been tried Gilbert and de Takats feel that considerable improvement follows such therapy if it is done within eight hours of onset Our experience includes only a few cases treated so promptly and results have not been impressive After twelve to twenty four hours stellate injection seems of little value

If patients are unconscious or disabled thrombosis cerebral hemorrhage and subarachnoid bleeding must be differentiated The signs and symptoms of increased intracranial pressure the rate with which neurologic change occurs and lumbar puncture usually accomplish this If a diagnosis of thrombosis is established within twelve hours of onset procaine injection of the stellate ganglia every eight to twelve hours may be helpful

During coma nursing care will help prevent infections and decubitus If unconsciousness lasts beyond twenty four hours daily injection of 300 000 units of procaine penicillin will lessen the incidence of respiratory and urinary tract infections Fluid intake should be maintained between 2000 and 3000 cc daily Electrolyte content of fluids should be governed by the degree of cardiac and renal disease that exists

As soon as possible patients should be out of bed for rehabilitation Rusk has emphasized that the degree of functional recovery among these people is directly proportional to the speed and diligence with which activity is established and physical therapy is applied He believes that within ten days or two weeks all patients should be restored to some degree of self sufficiency

The program suggested by Rusk is active and vigorous and is instituted as soon as the patient is seen The affected leg is supported by a posterior splint or footboard and sandbags so that footdrop and external rotation cannot occur Excessive adduction of the arm is avoided by placing a pillow in the axilla As soon as the patient is conscious and can cooperate, active exercises are begun Quadriceps setting of both limbs to preserve muscle strength should be practiced twenty to thirty times daily An overhead pulley with weights attached to clothesline rope permits active exercise of the paralyzed arm and thus discourages the development of periarthritis of the shoulder

Within twenty four to forty-eight hours after the last signs of advancing cerebral disease sitting and standing exercises should be established as daily routine With this preparation the patient will be ready for instruction in crutching and walking which should be furnished by a physical therapist

CEREBRAL HEMORRHAGE

The course of massive cerebral hemorrhage is usually and probably fortunately brief and death ensues within a few hours Those who survive beyond eighteen to twenty four hours should receive individual nursing care antibacterial agents and fluids to maintain optimum conditions if by chance bleeding ceases and the patient lives After hemorrhage is controlled Wechsler has found that arteriograms sometimes localize accumulated blood which can be removed surgically to permit rather dramatic improvement in neurologic function Such measures are heroic but when effective their use is justified

Rehabilitation of this group of patients is similar to that employed for those paralyzed by cerebral thrombosis

16. Respiratory Diseases

H. CORWIN HINSHAW

Pulmonary Tuberculosis

IT IS usually conceded that the solution of the complex problems encountered in the treatment of *active pulmonary tuberculosis* should be undertaken by specialists Furthermore, the prolonged and serious hazard of contagion often necessitates institutional care However, the physician engaged in general practice may be called upon to supply interim care to patients who are awaiting admission to a sanatorium or a hospital, and even more frequently he must supervise the aftercare of a patient for many months or years after his disease appears *to have* been arrested The great popularity of mass roentgen ray surveys has led to the discovery of many thousands of *patients whose pulmonary tuberculosis is* in a stage of uncertain activity, and the physician often is called upon to advise such patients on the best way of avoiding the reactivation of latent disease This is preventive medicine in its purest form and frequently involves the exercise of keen judgment and strictest attention to minor details *In many instances the family physician* is admirably qualified to understand problems of the patient s home life important *occupational stresses* and *environmental* hazards which the distant specialist may not comprehend

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ur detail These criteria will be discussed nder the following headings (1) roentgen graphic data (2) clinical data (3) bacteri logic data and (4) endoscopic data

Roentgenographic Data

Frequently it is impossible on the bases f a single examination to determine hether lesions of pulmonary tuberculosis re active Serial films taken at suitable ntervals (from a few weeks to a few months) may show that a lesion is progres ive If this is demonstrated, it is acceptable vidence that the disease is active and re quires treatment Serial roentgen ray exam nations of the chest may show that a lesion s improving This likewise is an evidence of activity and indicates the need for more areful management than if the lesion is table over prolonged periods Stability hat can be demonstrated roentgenograph cally is the desired objective and if films aken over many months or even years indi cate that the lesion has remained unchanged the physician's confidence in the future safety of his patient increases proportionally

The presence of cavitation in a tubercu lous lesion should be accepted as evidence of active disease and need for treatment often of a very direct and localized nature such as some form of collapse therapy In addition to progression retrogression and cavitation there are other roentgenographic criteria of the activity of lesions of pulmon ary tuberculosis—although these are very difficult to define

For example shadows of a flocculent na ture and of fairly wide distribution may be regarded as active lesions under many circumstances Likewise large dense shad ows with poorly defined margins and shadows of segmental distribution involv ing an entire lobe or segment may be justifiably termed active under some cir cumstances even without prolonged pe riods of observation There is a tendency, which is not altogether dependable for diagnostic purposes for lesions of more chronic and less active nature to appear high in the apex of the lung and lesions of more recent origin and greater potential activity to appear below the level of the clavicle and in the mid and basal portions of the lung fields Although it is unsafe to permit location of the disease to be a very strong factor in determining the activity of the process at times location will aid the physician in deciding how frequently and intently a lesion need be observed

Clinical Data

It cannot be repeated too frequently that the lack of clinical evidence for activity may be of little real significance Tubercu losis is dangerous and treacherous it may progress to an alarming stage before it produces any local or systemic symptom which can be recognized While negative findings are thus of little or no value posi tive findings may be of great value In addi tion to roentgenologic study a most meticulous history and thorough physical examination is required under all circum stances before any logical therapeutic regimen can be outlined When tubercu losis is known to be present fever is a finding which demands explanation be cause fever may be due to activity of the disease Lack of fever however is evidence of little or no value Patients with known lesions of tuberculosis should learn to use the clinical thermometer and when under observation keep a temperature chart for a period of at least several days Because postovulation elevation of morning tem perature occurs normally in women it is suggested that the temperature of tuber culous patients be taken in the late after noon hours during the week preceding an anticipated menstrual period

An elevated erythrocyte sedimentation rate has roughly the same significance as an elevated temperature It may be elevated

when fever is not present Although normal sedimentation rate may occur with active and progressive pulmonary tuberculosis an elevated rate demands explanation and frequently leads to suspicion of active disease This test is by no means self sufficient and should be regarded as but one of the various criteria which may influence the physician s judgment

The complaint of cough and expectoration the existence of pleural pain the presence of localized wheezing respiration, and the detection of râles may be clues of great value when active disease is suspected

Age sex and race must be considered when attempting to decide whether a lesion of pulmonary tuberculosis needs treatment Certain races particularly Negroes and orientals and the age group between adolescence and 30 years especially females require close observation because they appear to possess inferior ability to stabilize pulmonary tuberculosis

Physical examination of the chest was a highly developed art in past medical generations but modernists have been too prone to scoff at its value The presence of fine rales audible over a lesion of pulmonary tuberculosis has long been considered as an evidence of active disease Such rales should arouse suspicion but are not in themselves jutifiable reason to declare a lesion active and in need of treatment Many lesions of pulmonary tuberculosis particularly those associated with fibrosis and distortion of the bronchial tree may so interfere with drainage of secretions that rales may be present continuously over many years even though the disease is not active and progressive The time honored *procedures of inspection palpation* and percussion are part of every physical examination of the chest and yet such procedures rarely yield evidence of critical value in determining whether a lesion of pulmonary tuberculosis is active or latent

A poorly nourished fatigued and under weight patient with pulmonary tuberculosis is *commonly regarded* as being in greater jeopardy than one who is well nourished rested, or normal weight and with normal muscular tone but there are so many other contributory factors that such findings are of minor significance

Bacteriologic Data

Active disease cannot exist unless the tubercle bacillus is multiplying Under these conditions there is frequently a continuous or at least an intermittent discharge of bacilli into the tracheobronchial tree *An unremitting search for bacilli is an essential part of every examination* to determine the need for treatment of a lesion of pulmonary tuberculosis Modern methods of isolating and culturing tubercle bacilli have placed the bacteriologist in close partnership with the clinician in determining the need for treatment

The presence of tubercle bacilli when detected by some of the more sensitive methods is not necessarily proof that the lesion is in need of active treatment There is substantial agreement however that *patients with apparently latent nonprogressive* pulmonary tuberculosis who occasionally are found to have tubercle bacilli in their gastric contents are in greater danger of developing progressive disease than patients whose gastric contents have been found repeatedly devoid of tubercle bacilli Clinical management must be planned to provide maximal protection against reactivation of smouldering tuberculosis which has been demonstrated *in* this manner

Endoscopic Data

In recent years the bronchoscope has become an important instrument in the study of selected patients with pulmonary tuberculosis Undoubtedly bronchial mucosa is very frequently involved with a tuberculous inflammatory process when there is active

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Roentgenographic Data

Frequently it is impossible on the basis of a single examination to determine whether lesions of pulmonary tuberculosis are active Serial films taken at suitable intervals (from a few weeks to a few months) may show that a lesion is progressive If this is demonstrated, it is acceptable evidence that the disease is active and requires treatment Serial roentgen ray examinations of the chest may show that a lesion is improving This likewise is an evidence of activity and indicates the need for more careful management than if the lesion is stable over prolonged periods Stability that can be demonstrated roentgenographically is the desired objective and if films taken over many months or even years indicate that the lesion has remained unchanged the physician s confidence in he future safety of his patient increases roportionally

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Clinical Data

It cannot be repeated too frequently that the lack of clinical evidence for activity may be of little real significance Tuberculosis is dangerous and treacherous it may progress to an alarming stage before it produces any local or systemic symptom which can be recognized While negative findings are thus of little or no value, positive findings may be of great value In addition to roentgenologic study, a most meticulous history and thorough physical examination is required under all circumstances before any logical therapeutic regimen can be outlined When tuberculosis is known to be present fever is a finding which demands explanation because fever may be due to activity of the disease Lack of fever however is evidence of little or no value Patients with known lesions of tuberculosis should learn to use the clinical thermometer and when under observation keep a temperature chart for a period of at least several days Because postovulation elevation of morning temperature occurs normally in women it is suggested that the temperature of tuberculous patients be taken in the late afternoon hours during the week preceding an anticipated menstrual period

An elevated erythrocyte sedimentation rate has roughly the same significance as an elevated temperature It may be elevated

adequate Meals should be served at regular hours and under conditions as peaceful and attractive as possible A good phonograph a *radio* a *television* set good books, or other sources of diversion which interest the patient may prove to be good investments and actually *speed recovery*

Collapse Therapy

*Collapse therapy in pulmonary tuberculosis most nearly approaches a specific treatment for the condition in many clinical circumstances Unfortunately effective collapse of the lesion cannot always be attained because of the location and distribution of the disease, its extent or complications such as pleural adhesions However some type of collapse therapy can and should be applied to a considerable majority of cases of active pulmonary tuberculosis Which of the several available methods should be utilized frequently involves a difficult decision in which equally well qualified consultants may differ As a result, the choice of collapse procedure should be made by a physician with long experience and good judgment or better yet, after a conference between two or more physicians who are familiar with the handling of such problems

Pneumothorax The popularity of pneumothorax once regarded as an ideal form of collapse therapy has greatly declined in recent years This is not due to its ineffectiveness but to the very real risk involved in the frequently encountered pleural complications The induction and early maintenance of a pneumothorax cannot be carried out safely in the home Although ambulatory pneumothorax without a preliminary period of hospital care frequently involves serious dangers after the disease has become stabilized pneumothorax may be continued on an ambulatory basis usually for a few years One of the most difficult decisions is when pneumothorax may be abandoned with safety, and here again the opinions of well-qualified physicians will vary widely

Pleural adhesions constitute a serious complication of pneumothorax Unless these adhesions are so located that they can be severed by intrapleural pneumonolysis by manipulations through a thoracoscope their presence is frequently clear indication for the prompt abandonment of pneumothorax It is believed that most of the complications of pneumothorax therapy can be avoided if the unsatisfactory pneumothorax is abandoned very promptly and some other collapse procedure such as pneumoperitoneum substituted

Pneumoperitoneum. Pneumoperitoneum has increased in popularity greatly during recent years, but the procedure has not yet passed completely beyond the stage of controversy and experimentation While pneumoperitoneum is not devoid of hazard it is agreed that these hazards are much less than those accompanying pneumothorax therapy The indications for pneumoperitoneum therapy have not become established clearly Perhaps too often this procedure is utilized when no other effective measure seems to be applicable Under these circumstances of course end results will appear to be very inferior Some have reserved pneumoperitoneum for lesions of minimal extent or lesions of uncertain activity when it was judged that more radical collapse procedures were not justified A few have persisted in the belief that pneumoperitoneum is chiefly of benefit to lesions affecting the basal portions of the lungs Whatever measure of relaxation pneumoperitoneum affords the base of the lung is almost surely transmitted throughout the substance of the lung up to and including the apex, especially if the pleural space is free and there are no extensive restrictions to effective collapse such as might be afforded by dense fibrosis particularly such as occurs in silicosis Since pneumoperitoneum is a procedure which

disease in the parenchyma of the lung However, occasionally parenchymal disease may be nonprogressive and apparently latent together with an ulcerating and extending disease of the bronchial mucous membrane Establishment of the existence of such disease is of profound importance in assessing the patient s outlook and the choice of treatment, usually in the direction of more radical chemotherapeutic and surgical therapy

MANAGEMENT OF ACTIVE PULMONARY TUBERCULOSIS

Active progressive pulmonary tuberculosis is a serious threat to any patient s continued health and significantly shortens his life expectancy Therefore it is almost universally agreed that treatment should be instituted at the earliest possible moment Although it would be inappropriate—even if it were possible—to portray all the medical surgical and environmental measures in the treatment of pulmonary tuberculosis in this chapter, it would seem worthwhile to outline the objectives of (1) rest therapy (2) collapse therapy (3) chemotherapy including antibiotic therapy and (4) pulmonary resection

Rest Therapy

When the need for treatment has been established steps should be taken immediately to provide an environment which is as pleasant as possible and which affords complete physical rest and isolation from sources of nervous tension and anxiety It is exceedingly difficult to arrange such conditions in the average home despite the contrary opinion and protestations of the patient Rest therapy involves a certain discipline a philosophical conversion an altered view of life and these are more difficult to achieve under familiar surroundings The necessary complete change of habits is easier to attain when in the company of others facing similar problems The sense of frustration incident to being incapacitated in the home when others are able to follow their natural pursuits imposes a serious handicap upon the patient Many patients who have attempted treatment in both an institution and the home, assert that adaptation is more rapidly achieved in the former Certain patients are so constituted that proper rest under any conditions is unattainable If such persons develop serious progressive tuberculosis their outlook is distinctly more grave than that of persons able and willing to cooperate and develop a philosophy of passiveness serenity, and confidence

If treatment must be undertaken in the home as a temporary expedient while awaiting the availability of a hospital bed the cooperation of the patient s entire family is necessary Helpful service may be afforded by nurses especially those trained in public health work and experienced in assisting families to make the necessary alterations and sacrifices involved even for temporary periods The patient should be given a quiet room isolated from the rest of the house Entrance to this room should be forbidden to all except those caring for his needs Very careful instruction must be given to all with regard to the disposal of sputum and other possible sources of contagion The handling of dishes laundry magazines books and other articles may be important if the patient has a positive sputum and if housing conditions are less than ideal In a large majority of instances, greater progress toward recovery will be made if the bed rest is absolute and the nursing attention complete with the possible exception of a daily trip to a nearby bathroom for the regularly scheduled bowel movement

The diet should receive considerable attention with particular emphasis upon serving attractive food which fulfills recognized nutritional requirements Caloric, protein and vitamin intake should be fully

tional impairment, while appearing to yield cavity closure or extirpation, and adequate relaxation of diseased pulmonary tissue. Pneumoperitoneum most frequently satisfies these requirements when the degree of collapse required is but moderate and in those circumstances where bilateral collapse is needed. When the disease is largely unilateral and when considerable collapse appears to be necessary, a trial of pneumothorax likely will be undertaken first. Since pneumothorax is always an exploratory procedure during its initial phases, it may have to be abandoned when nonresectable pleural adhesions are revealed and a procedure of second choice substituted.

When the disease is of chronic, destructive localized character and of sufficient extent, primary thoracoplasty or pulmonary resection may be undertaken as the procedure of choice. When there is tuberculous bronchitis with stenosis pulmonary resection usually is the operation of choice. Blocked cavities spherical caseous lesions ("tuberculomas"), destroyed lobes, and cavities not responding to simpler measures also call for resection when the patient's general condition permits such radical surgery. Interruption of a phrenic nerve is recommended only as an auxiliary procedure, usually in association with pneumoperitoneum. Extrapleural pneumothorax should be reserved for those unusual circumstances where conservation of pulmonary function is a most important desideratum, where only localized collapse is required and other methods of treatment do not suffice.

Antibacterial Therapy

It has now been approximately ten years since the first antibacterial agents were developed which were capable of suppressing tuberculosis in experimental animals and, to a lesser degree, in man. The earliest drugs effective in this respect were derivatives of diaminodiphenylsulfone. These drugs have never attained wide popularity in the treatment of tuberculosis, but they have become the drugs of choice in the treatment of that other great mycobacterial disease, leprosy. The isonicotinic acid derivatives are active but have not been fully evaluated. The appearance of streptomycin in 1944 represented a distinct forward advance and has produced something of a revolution in the treatment of human tuberculosis.*

The practice of combining streptomycin with *p*-aminosalicylic acid ("PAS") has now become established as desirable in essentially all circumstances where both drugs are tolerated and when antibacterial therapy is necessary. This combined drug therapy has overcome, in part at least, many of the objections to streptomycin therapy which were so prominently voiced in the earlier literature on this subject. Combined therapy has reduced the hazard of development of strains of tubercle bacilli which are resistant to either of the drugs, resulting in a much prolonged period of effective action and in addition it has lessened the need for administration of highly toxic doses of either drug.

Streptomycin-PAS therapy is rarely definitive therapy and finds its greatest utility in combination with sanatorium care, collapse therapy, and resectional surgery. The trend has been to use such treatment in a substantial majority of all types of active progressive pulmonary tuberculosis, especially during the more acute phases of the infection. The trend is growing toward much more prolonged and less intensive drug therapy, such treatment being continued for at least several months and not infrequently for a year or more when a continuing need is manifest.

Ideally antibacterial therapy should be undertaken while the tuberculous disease is in its early, so-called "exudative" phase

* See also Chapter 4

carries very little risk, it seems plausible that it should be used much more freely in the future

Interruption of Phrenic Nerve Opinions vary widely concerning the indications for interruption of the phrenic nerve It is in general a procedure for predominantly unilateral tuberculosis and disease which is not in need of extensive collapse However, in combination with pneumoperitoneum, remarkably extensive collapse can be achieved at times

Thoracoplasty Thoracoplasty was once regarded as an extensive, serious and mutilating operation which should be reserved as a last resort for patients with extensive destructive disease This attitude has been altered appreciably during the past decade The operation need not produce serious deformity the operative risk has been reduced to a low figure Thoracoplasty affords a permanent collapse not attainable by any other method for chronic cavitating disease Pulmonary function is impaired but by no means abolished by thoracoplasty When thoracoplasty is no longer regarded as a last resort procedure, when its use is restricted to that group commonly called good chronics and when the operation is performed to collapse diseased segments effectively it will lose much of the terror with which it is regarded in some quarters At the present time, thoracoplasty is frequently utilized as the procedure of choice, and as a primary procedure not requiring a trial of the less definitive and less permanent forms of collapse

There are other methods of collapse therapy besides the ones mentioned above but these have not attained wide popularity in the United States Various surgical procedures to create an extrapleural pocket into which air oil paraffin plastic balls or other foreign substance is introduced have been advocated and abandoned repeatedly for many years At the present time, extrapleural pneumothorax is enjoying an unprecedented popularity in some European countries and we await their results with considerable interest since this procedure has never been tried extensively in the United States The introduction of oil into the pleural space has been largely abandoned in most institutions in this country

Pulmonary Resection

The development of antibacterial agents has been one of the important factors in making the thoracic cavity available to surgical exploration and radical surgical corrective measures Penicillin has decreased the incidence of pyogenic infections and streptomycin has made significant contributions in preventing the development of tuberculous complications following intrathoracic surgery on patients with pulmonary tuberculosis It would be out of place to attempt an adequate discussion of the indications for pulmonary resection in tuberculosis except to say that the lung or a portion of the lung should be removed when this can be accomplished without excessive risk and when the disease cannot be expected to heal by collapse therapy by chemotherapy alone, by any reasonable period of bed rest treatment or by any combination of these procedures Some of the commonly accepted indications for pulmonary resection include bronchostenosis destroyed lobes or an entirely destroyed lung giant cavities localized circumscribed, isolated lesions of tuberculosis often called tuberculomas and possibly tuberculous bronchiectasis

Choice of Collapse Therapy

Frequently any one of several methods of collapse therapy or pulmonary resection might be applied effectively to a given lesion of pulmonary tuberculosis The procedure of choice will be that method which involves the least risk of complications and which produces the least degree of func

streptomycin) and this best explains the otherwise unexplained inconsistency of results reported by different observers When the dose is but 1 Gm daily, there is no appreciable risk of any neurotoxicity if the patient has fully normal renal function If this dose be given intermittently, every two or three days, there is even less hazard involved

There are two other advantages to dihydrostreptomycin which deserve mention One is the fact that patients allergic to streptomycin may tolerate dihydrostreptomycin satisfactorily The other advantage lies in the stability of dihydrostreptomycin solutions permitting the distribution of the drug in solution, obviating the inconvenience of making sterile solutions immediately prior to injection

The controversy regarding the relative merits of streptomycin and dihydrostreptomycin has now almost completely subsided since smaller amounts of drug have been recommended and since intermittent treatment is often chosen Treatment carried out in this manner rarely produces any significant *toxic reaction* regardless of which form of the drug is chosen There is no acceptable evidence that either drug is more potent than is the other

The regimen recommended for the more serious clinical situations would involve 1 Gm of streptomycin or dihydrostreptomycin injected *in* one dose once *each day in*tramuscularly, combined with 12 Gm of PAS given orally as the sodium salt and divided into three or four doses during the day For less acute types of disease PAS is recommended in the same amount and the streptomycin drug is given only once in two or three days (1 Gm each dose) Treatment by either of these regimens may be continued for a year or more without interruption and the usual minimal duration of treatment recommended is six months Not infrequently the combined continuous regimen will be given for several weeks to be followed by several months of the combined *intermittent regimen* Clinical experience suggests that antibacterial drug therapy should be continued so long as favorable progress continues or until the desired therapeutic objective is attained Premature cessation of treatment may result in a relapse due to drug resistant bacilli which might not have been experienced had treatment not been suspended

p Aminosalicylic acid may be given without streptomycin but this is rarely advised now that the development of PAS-resistant tubercle bacilli has been demonstrated and since it is known that resistance to PAS may be prevented or delayed by concomitant use of streptomycin with no significant increase in toxicity When crucial types of tuberculous disease are due to streptomycin resistant tubercle bacilli it is possible to enhance the therapeutic effect of PAS to a marked degree by parenteral use of the sodium salt of the drug in large amounts The intravenous injection of dilute solutions (1–3 per cent) by continuous clysis may permit much more *intensive treatment than would be* tolerated by the oral route As much as 40 Gm each day may be given intravenously with no difficulty except for occasional local *venous thrombosis.* If adequate superficial veins are not available a plastic venous catheter may be inserted into a deeper *vein or the drug may be given* subcutaneously For subcutaneous clysis a 1 per cent solution is recommended and the local injection of hyaluronidase may facilitate absorption

MANAGEMENT OF INACTIVE PULMONARY TUBERCULOSIS

The specialist in thoracic diseases will usually manage the difficult phases of active tuberculosis, but his patient may *continue* to have so-called inactive tuberculosis for the remainder of his life Often he cannot or need not maintain contact with the

before extensive destructive changes have been wrought Unfortunately but few persons with tuberculosis seek care before serious damage to pulmonary tissue has occurred but usually there is a zone of exudative inflammatory reaction peripheral to the core of necrotic material At other times a whole lobe or pulmonary segment may become involved simultaneously, resulting in a tuberculous pneumonia which, if unchecked by antibacterial drugs, may produce irreparable damage Such pneumonia constitutes one of the most urgent indications for prompt treatment with streptomycin and PAS In selecting patients for treatment with these drugs the physician is guided largely by his judgment as to what proportion of the disease present is of the reversible type On other occasions his objective is only to so saturate the tissues with the antibacterial drugs as to discourage further advance of the disease process meanwhile definitive collapse or surgical measures are under way

The complications of pulmonary tuberculosis which affect the bronchial, laryngeal oral, or intestinal mucosa are most responsive to streptomycin PAS therapy especially when these are of ulcerative type Thus tuberculous bronchitis (as demonstrated bronchoscopically) tuberculous laryngitis and tuberculous enteritis constitute definite indications for drug therapy The less frequently encountered ulcerative lesions of the tongue of the buccal mucosa and of the oropharynx respond in a similar manner

The prophylactic use of streptomycin and PAS in conjunction with radical thoracic surgery in pulmonary tuberculosis has aided the surgeon greatly Pulmonary resection for tuberculosis formerly was hazardous largely because of the tuberculous complications resulting from surgical manipulations, especially empyema and bronchiogenic extensions of the disease When the tubercle bacilli are sensitive to streptomycin and PAS and the surgeon operates upon tissues containing these drugs in bacteriostatic concentrations, extensions of the disease rarely result In other instances drug treatment may so improve the patient s general condition that surgical treatment becomes possible The operations which require streytomycin prophylaxis are those which involve manipulation and removal of diseased tissue, such as pulmonary resection, decortication and cavernostomy Thoracoplasty rarely requires concomitant drug therapy unless there is acute disease present either on the homolateral or contralateral side

Streptomycin and dihydrostreptomycin both possess distinct and potentially serious neurotoxic potentialities but these are greatly reduced when the smaller doses now commonly used are chosen Both drugs have remarkably specific effects upon the eighth cranial nerve Streptomycin may affect either the vestibular or the cochlear branch of this nerve, but is much more likely to damage the vestibular branch When the average dose of streptomycin is about 1 Gm per day for four or more months approximately 10 to 20 per cent of patients will suffer some impairment of vestibular function, often permanent but rarely incapacitating When this dose is administered only once in every two or three days vestibular damage is very rarely observed

Dihydrostreptomycin was developed because it is much less toxic for the vestibular nerve and these observations have been confirmed repeatedly and consistently However, prolonged treatment with large doses of dihydrostreptomycin especially to patients with reduced renal function has apparently resulted occasionally in serious damage to the cochlear branch of the eighth nerve There is some evidence that this damage was partly or wholly the result of an impurity (possibly hydroxydihydro-

of tuberculosis should be considered at some point in the investigation of every pulmonary abscess regardless of how typical of a nontuberculous process it may be in its clinical and roentgenologic manifestations

Diagnostic Criteria

Pulmonary abscess may be defined as a nontuberculous localized destructive, cavitating suppurative inflammatory disease of the lung For therapeutic purposes it is best to classify pulmonary abscess according to the causative factors when these can be ascertained or surmised The causes of pulmonary abscess include (1) bronchial obstruction due to foreign body, carcinoma, inflammatory stricture blood clots within the bronchi (2) aspiration and retention of septic material within bronchi with local propagation of the infectious process, (3) blood borne infection especially septic embolism with infarction (4) destructive primary infectious processes such as Friedlander s pneumonia or transdiaphragmatic extension of an hepatic or subdiaphragmatic abscess (5) rupture of a pleural empyema pocket into the lung especially interlobar empyema and (6) so called bronchiectatic abscess secondary to the chronic pulmonary suppuration of bronchiectasis with a superimposed acute or subacute localized destructive inflammatory process *often the result of bronchial* stenosis

For practical purposes the three most important causes of pulmonary abscess are (1) *aspirational abscesses following* tonsillectomy under general anesthesia or dental surgery under general anesthesia, (2) aspirated foreign bodies especially in children and (3) bronchiogenic carcinoma, especially in adult males

The clinical syndrome of pulmonary abscess is characterized by either acute or chronic manifestations dependent upon the *causative factors Pulmonary* abscess related to surgery on the upper respiratory tract or the oral cavity rarely occurs unless a general anesthetic has been employed Pulmonary *manifestations usually occur* within a week or so following such surgery and their onset is often very acute with high fever, with chills sometimes without any early clear cut respiratory symptoms to indicate that the lung is the source of difficulty More frequently, from the beginning a dry cough and perhaps a pleuritic pain simulating the early stages of a pneumonia are present. After the abscess has fully matured, it is likely to rupture into a bronchus, often with alarming and dangerous suddenness, resulting in the expectoration of a vast quantity of pus which may nearly or actually drown the patient When pulmonary abscess is due to a foreign body within a bronchus there may be a sufficiently long latent period to make it difficult to relate the abscess to the aspiration of the foreign body which may have been remarkably well tolerated until the abscess supervenes When due to bronchiogenic carcinoma, pulmonary *abscess often* has a very slow and insidious onset resembling that of tuberculosis but on some occasions, the onset is so sudden that it leads to a diagnosis of acute pneumonia

The presence of a cavity is the outstanding roentgenographic characteristic of pulmonary abscess Usually an extensive inflammatory process surrounds the cavity *and casts a dense and rather homogenous* shadow on the film Rarely are abscesses multiple and when they are it is fair to assume a hematogenous origin

Treatment

The treatment of pulmonary abscess is not unlike that of comparable abscesses elsewhere drainage or excision and antibacterial therapy Surgical *intervention* is best delayed until after the most acute phase of the disease is completed *Whether* the surgeon chooses drainage or excision may depend on the patient s age and general condition and upon the location and

specialist during this prolonged period, and in many communities, such specialists are available only to patients while they are in an institution. Therefore, it becomes the duty of the general practitioner, the internist, and some specialists in other fields to guide these patients wisely.

The patient with inactive tuberculosis is in a position of greater safety as the period following cessation of activity of the disease increases. Unfortunately, he must regard reactivation as an ever-present hazard, but the degree to which this is emphasized depends greatly on individual circumstances, the amount of disease which was present, the completeness with which treatment was undertaken, and the apparent effectiveness of such measures. Age and race also play a part. Certainly the patient in the second and third decades of life is in greater danger; certainly the pregnant woman faces a serious risk; certainly the person who must carry out heavy manual labor or who is placed under other great physical stresses faces increased hazard. As in so many aspects of medicine, judgment on the part of the physician may determine how long this patient may escape reactivation of disease. Perhaps equally important is the need for recognizing any reactivation of the disease at the earliest possible moment. Of the various aids which may help in such early recognition, the roentgenogram holds paramount place. A patient with recently active tuberculosis must have roentgenographic examinations of the chest every few months, and, as lesions remain stable for prolonged periods, this interval may be prolonged, but the need for periodic roentgenography can never be abolished by time in many instances.

The physician must develop a genuine interest in the patient's habits of work, rest, and play. He must develop an interest in well people as well as in sick people. He must possess rare patience and tact. While being constantly on the alert for trouble, he must help his patient avoid the development of a psychoneurosis or anxiety complex. This requires more time and patience than many possess.

Pulmonary Suppurative Diseases

PULMONARY ABSCESS

Pulmonary abscess is one of the more serious infectious diseases of the lungs. Its proper management requires [illegible] ... [illegible] and the thoracic surgeon. Improvements in antibacterial therapy and in thoracic surgery have made some older concepts obsolete. Possibly, further advances in these fields will quickly modify the opinions expressed in this chapter.

Pulmonary abscess is so frequently a secondary phenomenon that the physician invariably points his efforts in a diagnostic direction whenever the possibility of pulmonary abscess is presented. Certainly the management of pulmonary abscess is very different if it is due to an obstructing bronchogenic carcinoma, or an aspirated foreign body, or pulmonary infarction, or if it is secondary to staphylococcic bacteremia. Management will be entirely different if the disease is a few days', weeks', or months' duration. Treatment will be modified by the presence of such complications as empyema, pulmonary hemorrhage, and aspiration of the infectious process into other pulmonary segments. The possibility

and putrefaction of secretions within the multiple abscess cavities and the dilated bronchi which have been deprived of their normal functions The amount of such drainage may reach enormous proportions and may involve the loss of considerable nitrogenous exudate In addition the clinical manifestations of chronic sepsis may be utterly debilitating However, the patient s presenting and unremitting complaint is the foul odor of the sputum which may be most offensive and which may isolate the victim from social and business contacts All efforts to mask this odor will fail and if relief is to be granted, some method of controlling the infectious process must be devised or, if possible, the offending organ removed

Treatment

Selection of cases for pulmonary resection The surgeon the roentgenologist, and the internist will collaborate closely in determining if a given case of bronchiectasis is operable Ideally, surgery will be offered only to patients with unilateral bronchiectasis preferably restricted in distribution to a single lobe but exceptions to this rule frequently are made When the left lower lobe is involved, the lingular segment of the left upper lobe is also likely to be diseased and to require segmental resection At times the middle lobe on the right side may be involved with the right lower lobe Removal of an entire lung for bronchiectasis is more frequently carried out in recent years than formerly and some times with excellent results especially in younger persons with disease of long duration Rarely, bilateral lobectomy has been accomplished It should be remembered that when a lobe is completely involved in the septic process, its function as an organ of respiration is largely or totally destroyed and resection may not produce any significant limitation of respiratory reserve In deed patients have experienced less dyspnea after removal of an entire lung for bronchiectasis than previously perhaps because after operation all pulmonary circulation was directed to a good source of oxygen supply

Upper lobe bronchiectasis often produces clinical manifestations very differently from those resulting from involvement of basal segments Bronchorrhea which plagues the victim of lower lobe bronchiectasis may *not* exist at all when a similar amount of disease is present in an upper lobe Perhaps this is due to the favorable effect of gravity drainage of bronchi directed upward, thus preventing accumulation and putrefactive decay of pulmonary secretions Upper lobe bronchiectasis may go undetected until pulmonary hemorrhage makes a surprise appearance Isolated upper lobe bronchiectasis may not require pulmonary resection if symptoms are not severe

Symptomatic Treatment The offensive and demoralizing quality of the symptoms of bronchorrhea justify diligent and protracted therapeutic efforts Even though the underlying disease is not cured the occasional excellent result achieved by present day medical therapy is ample reward for prolonged and difficult effort Treatment of inoperable bronchiectasis should be directed simultaneously toward drainage restraint of microbial multiplication and mobilization of body defenses by such means as rest, proper nutrition, and favorable climate

Drainage of secretions is poorly accomplished by the cough mechanism under the handicap of bronchial distortion and dilatation, the loss of ciliary action of respiratory epithelium and the opposing force of gravity Only the factor of gravity may be opposed and even brought to the aid of the patient by the simple maneuver of postural drainage It is necessary to explain to each patient, patiently and repeatedly that *effective expectoration* can be accom

extent of the disease In younger patients with evidence of destructive disease limited to the central portion of a single lobe, lobectomy is the procedure of choice However, if the disease is well localized and clearly peripheral with minimal evidence of destruction, and if the patient is older or in poor physical condition external drainage may suffice Too frequently the procedure of external drainage is not adequate to avoid permanent localized bronchiectasis, but this may be unavoidable Resection is more likely to be chosen when the possibility of carcinoma is still entertained

Antibacterial therapy may abort an incipient pulmonary abscess if utilized early and intensively * All surgical procedures should be carried out under the protection of antibacterial therapy Procaine penicillin in large doses (minimum 600,000 units daily), often combined with streptomycin (1 Gm daily) should be employed for many days whether intended as a definitive treatment or as an auxiliary therapeutic procedure Chloramphenicol aureomycin or terramycin may effect a therapeutic response when penicillin fails and some physicians prefer to employ one of these routinely It is most desirable to determine by cultural means which of these drugs most effectively suppresses the bacterial flora present

Bronchoscopy to search for foreign bodies carcinoma, and bronchial strictures should nearly always be carried out when pulmonary abscess is present Occasionally *an excellent therapeutic result may be* achieved by bronchoscopy as an internal drainage procedure, combined of course with prolonged appropriate therapy

BRONCHIECTASIS

Bronchiectasis is precisely what the name implies a dilatation of bronchi The dilatation is the result of destructive inflammatory processes destroying the normal supporting structures of the bronchial walls Such a process is irreversible and it is doubtful whether dilated bronchi can ever approach a normal state or function A fair estimation of the significance of bronchiectasis is contained in the statement that severe bronchiectasis dating from childhood carries about the same clinical outlook as does severe rheumatic heart disease, with a similar reduction in life expectancy For this reason vigorous therapeutic efforts are fully justified despite the lethargy and discouragement with which such problems are often approached by physicians, patients, and relatives alike Therapy somewhat hazardous to life (pulmonary resection) and expensive, uncertain therapy (antimicrobial, hospital, and climatic therapy) may be fully justified under such circumstances, even though it may require institutional care and expenditure of public funds

Bronchiectasis can be treated intelligently only when the character, extent and distribution of the disease process has been well defined This requires the instillation of iodized oil into each of the bronchopulmonary segments for roentgenographic studies, carefully prepared and expertly interpreted Complete lung mapping is essential if surgical resection is being considered but if there is some distinct contraindication to radical surgery less complete investigation may suffice

Whether the bronchial deformity of bronchiectasis is of a saccular or cylindrical type is less important than the clinical se*verity of the manifestations of the disease* The quantity and character of the sputum, the effect of the infection upon the patient's health and social life the co-existence of sinusitis or other complication are factors which determine whether treatment need be undertaken and how energetically therapy must be promoted

Bronchorrhea, often profuse and foul is the symptom against which therapy usually is directed It is caused by the accumulation

* See also Chapter 4

terramycin chloramphenicol or aureomycin The bacteriologist may be of great assistance *in solving the problem of choice* of drug by culturing the sputum in media containing various antibacterial drugs to *determine which will most completely* inhibit the flora of a particular patient at a particular time It is important to realize *that extensive shifts in bacterial population* may occur following even brief periods of treatment and that appropriate shifts in *therapeutic strategy must be undertaken*

If systemic treatment is unsuccessful after thorough trial of several weeks of intensive therapy *utilizing maximal toler*ated doses of appropriate drugs consideration should be given to direct local, topical, intrabronchial administration of the antibacterial drugs These may be administered either by (1) aerosolized solutions (2) micronized powder or (3) transglottic insullation

The inhalation of finely divided liquid particles of penicillin and streptomycin solution by *aerosol* permits the penetration of the drug directly to *the smallest ramifi*cations of the tracheobronchial tree where an effective antibacterial concentration of *the drug may be achieved There is consid*erable difference of opinion among physicians as to the true value of this procedure *in treating the symptoms of* bronchiectasis Treatment should not be undertaken un*less the patient* is willing and able to make such treatment a full time task perhaps for several weeks Only after such a thorough intensive trial has been completed can it be said that the method is valueless

Aerosol therapy is by no means univer*sally applicable and it is not always pos*sible to predict when it may be successful Those patients with bronchiectasis who *also have extensive* emphysema seem to be least likely to benefit This is probably due to the relatively poor exchange between tidal air and the large body of residual air the latter being in contact with the areas of infection This is *perhaps the reason* that older patients seem to benefit less frequently than do the younger patients

Effective aerosol therapy requires good equipment, adequate time and intelligent cooperation by the patient The equipment must include either an oxygen tank to serve as a source of motive power in expelling the aerosol or a motor-driven blower A tank of compressed oxygen seems preferable because it is inexpensive and it *is quite possible that the inhalation of oxy*gen with the aerosol may be of some benefit in discouraging the growth of putrefac*tive micro-organisms which are often par*tially anaerobic However, such possible superiority of the oxygen method has by no *means been demonstrated It is essential* however, whatever the motive power that it be capable of vaporizing 1 cc of penicillin and streptomycin solution within five to ten minutes It is extremely difficult—if not utterly impossible—to vaporize such volumes of solution in an effective manner by means of the conventional hand bulb *which is supplied with each nebulizer* Several types of nebulizers which are well adapted to the aerosolization of solutions are available from different manufacturers There is some variation between individual nebulizers of the same brand and the ability of a given instrument to vaporize the solution rapidly enough should be tested before the patient undertakes a *program* which may involve several weeks of his time and a considerable amount of money

The mist delivered by a nebulizer is so fine and transparent that it is invisible except when viewed by oblique lighting against a dark background The amount of oxygen or air flow should be adjusted to produce a visible fog of solution *when* viewed in such a manner It is well to time the amount required for the delivery of 1 cc of solution and learn to *adjust the ap*paratus so that this amount will be delivered in five to ten minutes To avoid loss

plished only with the aid of gravity This requires that the tracheobronchial tree be inverted, at least partially, when cough is undertaken

The standard position for postural drainage is with the patient's legs, extended across a high bed or a low table, his body flexed at the hips, the entire trunk inverted and supported with the hands on the floor It must be emphasized to the patient that the object is to invert the thorax, not merely the head, repeating that he is to cough with the force of gravity aiding, not hindering bronchial drainage In this position he will cough until no more sputum is available, then remain in this pose until a further supply appears and continue this until his respiratory passages are cleared This may require ten to twenty minutes, rarely longer, and considerable patience and perseverance are necessary A practical suggestion is to recommend that an isolated site be chosen where others will not be offended (basement attic barn), that newspaper be spread on the floor to receive the expectoration and subsequently be burned, and that generous time be allowed This maneuver must be repeated as often as necessary to keep the bronchi clear At the inception of the program, it is well to advise the patient to abstain from work for a few weeks and to make this his full time job re emphasizing that all his coughing is to be done in the inverted position The minimum requirement is that postural drainage be repeated four times per day, before each meal and at bedtime

Some patients find that elevating the foot of the bed at least eight to twelve inches may avoid the excessive accumulation of sputum during the night Others learn some odd posture which is peculiarly adapted to effective gravity drainage of secretions in his particular circumstances

The viscosity of secretions may greatly hinder gravity drainage of thick, even semi solid, plugs of sputum Expectorants such as potassium iodide in ascending doses, may vastly improve the results of postural drainage Also the patient should be urged to force fluids (4000 cc or more daily) by mouth If iodides are not tolerated, other expectorants such as ammonium chloride may be tried, but the objective of medication is liquefaction of sputum and often very large doses are required If the patient understands the purpose of the prescription he can greatly assist in the regulation of dosage and the choice of drug

Bronchoscopy may be of significant value in providing a clear drainage pathway through larger bronchi when bronchial stenosis is present Furthermore, bronchoscopic examination is often desirable to assist in excluding the presence of foreign bodies or tumors as a cause for localized bronchiectasis

The purpose of *antimicrobial therapy** is to restrain the growth of putrefactive microorganisms which abound in the veritable cesspools associated with bronchiectasis Systemic treatment (oral or parenteral) is much more convenient than the local application of the antimicrobial drugs into the tracheobronchial tree by means of aerosol mists and other methods described below The development of drugs with a broad antibacterial spectrum which may be administered orally has simplified treatment but these drugs (chloramphenicol, terramycin aureomycin) may facilitate the growth of *Monilia candida* and produce a situation which is difficult to control

A therapeutic regimen involving the use of procaine penicillin (600,000 units daily intramuscularly) streptomycin (1 Gm daily intramuscularly) and triple sulfonamide mixture (2–4 Gm daily by mouth) should first be tried If this program does not accomplish a marked reduction in the quantity of purulent sputum within two or three weeks of continuous treatment, consideration should be given to the use of

* See also Chapter 4

of penicillin and streptomycin It is necessary to apply a topical anesthetic agent to the larynx to permit the instillation of solutions directly into the trachea With some patients the amount of anesthesia required is very small and may not constitute a serious obstacle to the utilization of this method once each day at least for a limited period of time However a very serious objection to this method is that it does require an excess of medical attention and hence is rarely practical for many weeks of treatment Usually it is possible to instill from 1 to 5 cc of solution containing from 100 000 to 400 000 units of soluble penicillin and up to 0 5 Gm of streptomycin

The use of antimicrobial agents in the treatment of bronchiectasis is of course, but a palliative procedure and in no way affects the deformity of the bronchial passages responsible for the infection For this reason a recurrence of the infection usually associated with an acute cold is to be expected Hence every effort must be made by patients who have secured a good result from treatment to avoid respiratory infections Usually it is wise to undertake at least a brief period of penicillin and streptomycin treatment whenever an acute respiratory infection is contracted All of the occupational and climatic factors which go into the propagation of respiratory infections should be considered by the physician in such situations

Climate rest and *nutrition* are important elements of therapy The patient with uncontrolled septic bronchiectasis and profuse bronchorrhea is often a sorry spectacle of malnutrition Frequently little can be done to improve his nutritional state until the infection is in some sense controlled At times questioning will reveal that the discouragement and depression of such patients has led to poor dietary habits which may be accentuated because the repulsive odor emanating from such patients may prevent their eating with other people To avoid association with others patients with foul bronchiectasis may develop a habit of seizing some convenient food when hungry, giving little thought to the need for a well balanced diet

Rest has been thoroughly established as a valuable method in the treatment of pulmonary tuberculosis Scant attention has been given to the use of body rest as a treatment for other chronic pulmonary conditions such as bronchiectasis There is no known justification for utilizing complete bed rest in the treatment of bronchiectasis but it seems evident that many patients with this chronic debilitating disease need much more rest in bed than does a normal person Although bed rest must be highly individualized a minimum of twelve hours out of each twenty four should be spent in bed by those suffering from systemic symptoms of bronchiectasis The best division of such time is ten hours of rest at night and a two hour rest period following the noonday lunch To insure complete relaxation it is best that the patient lie undressed in a quiet darkened room during the noon rest period Most patients will eventually learn to secure some sleep during this interval and a small dose of phenobarbital (30 mg) may be helpful

Climate has been emphasized so much as a method of treating bronchiectasis that it will be minimized here Certainly, climate is not an important factor in some patients while others have secured great benefit by moving to an area where the relative humidity is very low winters are mild and sunshine is abundant Patients with inoperable bronchiectasis who have not been able to secure satisfactory control of their infection by postural drainage and antimicrobial therapy should be encouraged to try residence in a warm dry climate Before making great sacrifices which may be entailed in a permanent change it is well

of solution while the patient is exhaling, a Y tube should be inserted between the oxygen tank and the nebulizer to which an open rubber tube is attached. The patient holds his thumb over this open tube while inhaling but when exhaling he releases the thumb pressure permitting the oxygen to escape without passage through the nebulizer. Within a few hours nearly all patients can learn to operate the apparatus automatically.

The patient should prepare the solution immediately before use by adding a soluble tablet containing 100 000 units of sodium penicillin G to 1–2 cc of solution containing 0.1–0.25 Gm of streptomycin.

If aerosol therapy is to be truly effective it is desirable to maintain an antibacterial concentration of the penicillin and streptomycin in the bronchial secretions and exudates continuously for as many hours of the day as possible. Often it is not sufficient for the patient to saturate his secretions with the antibacterial drugs two or three or even four times a day. Instances where such treatment was ineffective have occurred but a good result was achieved by increasing the frequency of administration to six, eight or ten times a day. It is desirable that the patient who is to undertake such treatment should secure vacation from his work for at least two or three weeks and that he should plan to spend ten to twenty minutes of each hour inhaling the aerosol, continuing to do this for ten hours per day. Thus if he aerosolize 2 cc of solution per hour, each cubic centimeter containing 50 000 units of penicillin and 0.1 Gm of streptomycin, he will have received 1 000 000 units of penicillin and 2.0 Gm of streptomycin in ten hours. Such intensive therapy is by no means always necessary, but if the method is to be put to real test, the first course of treatment should be as intensive and prolonged as possible.

The patient should be advised to save all sputum expectorated, collecting this in a glass jar for the physician's inspection each day. In this manner the quantity and character of the secretions can be observed and any improvement clearly demonstrated.

Terramycin, aureomycin and chloramphenicol are useful in treating bronchiectasis and it is probable that terramycin is preferable. Frequently the bacteriologist can give useful information to the internist by cultivating organisms in sputum upon media containing various antibacterial drugs.

The use of *finely powdered micronized penicillin* for treatment of upper respiratory tract infections has attained considerable popularity because of the ease with which such material may be self-administered by patients. Such preparations cannot replace the aerosol method in bronchiectasis, however. An unduly large share of penicillin powder is deposited in the mouth and upper air passages, failing to reach the finer ramifications of the bronchial tree. Nevertheless the simplicity of administration of micronized powder has much to recommend it and it is certain that some patients may respond to this form of treatment. When for any reason an intensive program of aerosol therapy is impractical, a course of treatment with micronized penicillin powder might first be attempted. However, if this fails, it does not prove conclusively that the patient's disease is totally unsuitable for penicillin treatment.

A minimum of 200 000 to 400 000 units of powdered penicillin should be administered each day, involving expenditure of considerable time and effort. Some patients learn that the use of aerosol as described in previous paragraphs is less fatiguing and surely more effective than is the use of powder inhalations.

Some patients who have not responded to inhalation of penicillin have improved from *transglottic instillation* of solutions

a more empirical approach is sometimes justified Often it is possible to bring a serious acute pulmonary infection to a state of clinical arrest long before a bacteriologic laboratory can complete adequate studies, nevertheless sputum specimens should be submitted for microscopic and cultural study whenever a diagnosis of pneumonia is tenable If the patient appears to be dangerously ill blood cultures should also be performed

Patients with acute symptoms referable to the lower respiratory tract who are expectorating obviously purulent sputum should be subjected to minimal bacteriologic investigation when facilities are available A dried smear of such sputum stained by Gram s method may inform the physician whether the sputum contains gram positive cocci probably sensitive to penicillin or small gram negative bacilli (possibly Friedlander s bacilli) probably sensitive to streptomycin In either event the consulting bacteriologist will wish to proceed with cultural studies but the physician should not await the results of such studies before instituting what appears to be appropriate treatment The absence of bacteria in smears of sputum does not exclude the possibility of bacterial pneumonia

Serologic methods including determination of cold agglutinins may yield useful *information however such refined studies* are not always available They may not be necessary and are not entirely dependable, for cold agglutinins may appear too late in the course of the disease to be of value in directing treatment

The fact that such a large proportion of pneumonias respond so favorably to penicillin therapy tempts the physician to be casual in his approach to the treatment of this group of diseases despite the well known statistical evidence that a significant mortality rate from pneumonia persists The development of effective therapeutic agents against some virus and rickettsial types of pneumonia adds to the responsibility of the physician and the bacteriologist, and offers the research worker an important task for the development of more rapid and accurate diagnostic procedures

No consideration of acute pulmonary infection with symptoms of pneumonia would be complete without mentioning that pneumonia may be caused by tuberculosis and by bronchial obstruction due to bronchiogenic carcinoma or foreign bodies It is unusual to encounter a patient with an obstructing bronchiogenic carcinoma not diagnosed as pneumonia often because of striking temporary clinical success from treatment with penicillin In such instances, the carcinoma has actually produced an obstructive pneumonia and the infection may well be sensitive to penicillin For this reason patients who have experienced symptoms of pneumonia should have roentgenologic studies carried out after recovery to secure evidence that there is no detectable residual disease present This is particularly desirable if there are any physical signs to suggest bronchial obstruction if there is a history of grossly bloody sputum, or if the symptoms are of insidious onset It is important to recognize tuberculous pneumonia because of its prompt response to antibacterial therapy if treatment is early and because tremendous *destruction of pulmonary* tissue will ensue if treatment is long delayed

TREATMENT OF PNEUMOCOCCIC PNEUMONIA

Pneumococcic pneumonia has been deprived of much of its terror but when mortality statistics are consulted it is surprising to learn mortality from this disease still occurs despite effective weapons in the *form of modern antibacterial drugs* This mortality may probably be attributed to the complications of the disease often related to those physiologic handicaps imposed by reason of age chronic alcoholism

to suggest that a few months be devoted to a trial before transferring permanent residence

Sinusitis and Bronchiectasis The frequent association between infection of the paranasal sinuses and bronchiectasis is well known and offers special problems which usually can be solved only by careful collaboration between the otolaryngologist and the internist If there is obstruction to the drainage of infected sinuses, surgery may be desirable, but often it is wise to postpone operation until the bronchial infection has been brought under control if possible Frequently the sinusitis improves spontaneously as a result of measures directed toward the treatment of bronchiectasis However, residual sinusitis is to be avoided lest it serve to reinfect the bronchi following effective treatment

Prognosis

Bronchiectasis is by no means a hopeless disease In some instances, the source of infection may be removed by modern surgical methods, in others, the infection may be controlled, partially or completely, by simultaneous utilization of systemic postural drainage, antimicrobial therapy, general hygiene, and environmental therapy

It is important to re emphasize that no one method is of itself sufficient for all cases of bronchiectasis Usually it is necessary to employ all medical methods of treatment simultaneously in patients with inoperable bronchiectasis At least one half to two thirds of all patients with inoperable bronchiectasis may secure an encouraging measure of relief by the intelligent and persistent use of methods developed during recent years and described on the preceding pages

Pneumonia

THE presence of pneumonia may be determined by roentgenography long before the classical physical signs of pulmonary consolidation make their appearance For this reason it is urged that patients with acute pulmonary symptoms who are confined to hospitals should have immediate roentgenographic examination regardless of the presence or absence of physical signs This permits a more accurate appraisal of the clinical situation than can be obtained by physical examination alone However some patients with such symptoms will of necessity be seen in their homes where roentgenographic equipment is not available and therapeutic efforts may be instituted immediately without precise diagnosis

Much has been written attempting to define the differential characteristics of bacterial pneumonias as distinguished from the nonbacterial or primary atypical pneumonias Such differentiation is rarely possible on clinical or roentgenologic grounds except during epidemics where symptoms are characteristic and experience with recent cases may be valuable in the management of a given problem This may require careful clinical judgment and keen observation but is a practical and realistic approach

Treatment of pneumonia is directed primarily toward the etiologic agent, therefore it is universally agreed that recognition of the causative agent should be an important task of the physician * *Practical considerations*, on the other hand, sometimes make this impossible, and extensive experience by many physicians has demonstrated that

* See also Chapter 4

amount of antibacterial drugs may be reduced to one half the amount recommended above two or three days after the temperature has become normal

The antibiotics which possess a broad spectrum of antimicrobial action (chloramphenicol terramycin aureomycin) may be used in treatment of pneumococcic pneumonia with excellent promise of success Such therapy will be reserved for those circumstances where the physician suspects that the infection may be of viral origin because the side effects of treatment are likely to be unpleasant and because there is good reason to doubt if these drugs are as effective as those recommended above Furthermore, these drugs are more likely to lead to the appearance of monilial infections of the mucous membranes of the mouth, rectum vagina and intestinal tract

Complications

Pleuritis Pleuritis is a common complication by reason of the extension of the infectious process to involve the visceral pleura Usually there is a fibrinous exudate on the surface of the diseased lung and frequently at least a small amount of fluid in the pleural space Massive effusions are more rarely encountered now that pneumonia is so frequently treated early with antibacterial agents A persistent pleural effusion following what may have appeared to be an acute respiratory infection should always lead to suspicion of tuberculous pleuritis

Empyema Empyema is seen only occasionally in patients who have been well treated with antibacterial agents and when it does develop, It is more likely to be restricted to small pockets in the pleural space or in the interlobar fissures Treatment of empyema by intrapleural injections of penicillin solutions is likely to be effective only when the disease is treated at a very early stage The inaccessibility of multiple pockets often makes adequate local intrapleural treatment impractical Surgical drainage of well-developed empyema is required very frequently Treatment by aspiration and penicillin injection *should not be continued if there* is any clinical or roentgenographic evidence of uncontrolled pleural infection When pleural aspiration is being carried out for diagnostic purposes it is wise to have a solution of crystalline penicillin available in a concentration of 100 000 units per cc. to be injected in an amount of 5–10 cc even though a bacteriologic diagnosis is not yet available If intrapleural treatment is indicated, it is recommended that 500 000 units be injected every alternate day after aspiration of as much fluid as possible

Pericarditis Pericarditis is a rather rare complication of pneumonia but may be a very serious development which may escape detection by usual methods of physical examination When pericarditis is suspected, it is important that the dose of penicillin be maintained at a very high level at least 2,000 000 units per day The intrapericardial injection of penicillin solutions may be required, utilizing a solution containing 100 000 units of penicillin per cc of saline as was recommended in the treatment of empyema

Surgical consultation is desirable whenever there is pleural or pericardial infection present In such circumstances it is suggested that the surgeon help to bear the responsibility of therapy relatively early

Since pneumococcal pneumonia is not always a local disease but may be systemic often with large numbers of pneumococci demonstrable in the peripheral blood it is not surprising that many complications may occur when patients have not been adequately treated Among these complications must be mentioned endocarditis meningitis pneumococcus arthritis pneumococcal peritonitis and pulmonary abscess Each of these complications presents special problems making it difficult to formulate rules which would cover all

concomitant cardiac disease, or pulmonary abscess and empyema which might have been prevented had the patient sought medical attention earlier Mortality statistics cannot distinguish between the nonbacterial and the bacterial pneumonias and, of course, they do not differentiate between the various pneumonias caused by different bacterial species Furthermore, a considerable number of fatalities not properly attributable to pneumonia are included in the mortality rate for pneumonia These include pulmonary embolism, pulmonary edema of cardiac origin, obstructing bronchial lesions including carcinoma and perhaps a host of extrathoracic diseases Despite all these imperfections of statistics we must admit that people still die of pneumonia and pneumococcic sepsis, therefore the responsibility of the physician attending a patient with pneumococcic pneumonia is still heavy

Treatment

Diplococcus pneumoniae is sensitive to penicillin, sulfonamides chloramphenicol, terramycin aureomycin and streptomycin Not all strains of the pneumococcus are sensitive to the three latter named drugs and it is widely conceded that the drug of choice is penicillin either alone or combined with sulfonamide or with streptomycin There is some experimental evidence to indicate that it may not be wise to combine penicillin with chloramphenicol terramycin or aureomycin although the clinical implications of these experiments have not been elucidated as yet

Penicillin Fortunately there is no recognizable upper limit to the clinical dose of penicillin and the drug is tolerated by most persons except those possessing a true allergy to the antibiotic This greatly simplifies the task of the physician and permits him to select a regimen based upon the apparent severity of the infection and to employ doses sufficiently large to enter the realm of actual bactericidal action During the acute phase of the infection the minimal dose suggested for treatment of pneumococcic pneumonia is 300 000 units of procaine penicillin every twelve hours injected intramuscularly The addition of crystalline penicillin, 100 000 units every twelve hours provides some additional fortification and increased promptness of action If gram stains of the sputum indicate that there is a mixed infection present, streptomycin (or dihydrostreptomycin) 0 5–1 0 Gm every twelve hours may be added in order to discourage the overgrowth of other micro-organisms There is also some experimental evidence to indicate that the bactericidal potency of penicillin against some micro organisms may be enhanced by the addition of the streptomycin drug Mixtures of procaine penicillin and crystalline penicillin with or without dihydrostreptomycin, are available commercially in convenient forms

Sulfonamides The sulfonamide drugs constitute fully adequate specific therapy for most patients with pneumococcal pneumonia but the unpleasant side effects frequently experienced when large doses (more than 6 Gm daily) are administered has diminished the popularity of such treatment Smaller amounts of sulfonamide mixtures, 1 Gm every six hours may be tolerated well and may potentiate the action of penicillin when administered concurrently, as well as broadening the antibacterial action to include accompanying micro organisms Such mixtures of sulfonamide drugs include proper proportions of sulfadiazine combined with more soluble sulfonamides (sulfamerazine, sulfamethazine, sulfacetimide sulfapyrazine) to diminish the hazard of renal concretions

Antimicrobial therapy in pneumonia should be continued for at least seventy two hours after the temperature returns to a normal level, but if there is any suggestion of impending complication such treatment should be continued for a longer period (seven to ten days) usually the

17. Gastrointestinal Diseases

RUSSELL S BOLES

ASIDE from certain specific infectious conditions such as the dysenteries tuberculosis syphilis and some types of hepatitis the cause of most disorders of the digestive tract is unknown and probably nonspecific Examples of this type of disorder are peptic ulcer, gallstones pancreatitis regional enterocolitis chronic idiopathic ulcerative colitis irritable colon diverticula appendicitis polyps and carcinoma As the symptoms of many of these are largely the result of disturbances in the motor and secretory functions of the tract treatment must be designed to restore as far as possible normal tone motility and secretion The etiology of disorders not due to specific infections is mostly presumptive and the explanation of many of the more frequently encountered symptoms is still wanting Consequently treatment cannot be exact and failures in treatment are discouragingly common

Many disorders of the digestive tract are purely functional As such they are amenable to sound conventional therapy Organic disorders might well be as responsive if the patient is conscientiously studied and if his background disposition habits and all the many traits that comprise his personality are learned Scientific technics will avail little when personal technics are lacking only by an experienced blending of both can the patient best be served

Diseases of the digestive tract that primarily require surgery are not discussed in this chapter Particularly, this includes appendicitis tumors of the stomach and intestines and anorectal lesions of a surgical nature

In the case of most diseases of an idiopathic or nonspecific type that affect the digestive tract it is only fair to the patient to consider with good conscience whether new and expensive drugs and antibiotics with unpredictable effects are really necessary and if the merits they possess justify their selection over older and well tried remedies Likewise indiscriminate employment of operations that are highly unphysiologic and whose effects are still unknown cannot be condoned In short therapy for gastrointestinal disease in most cases must of necessity continue to be conservative if improper or injurious practice is to be avoided and the ultimate interests of the patient best assured

situations It should be mentioned that sulfonamides should be added to penicillin when treating pneumococcal meningitis because penicillin does not diffuse readily into the cerebrospinal fluid The treatment of these complications will be described elsewhere in this book

Whenever pneumococcal pneumonia fails to respond promptly and dramatically to antimicrobial therapy within forty eight hours the physician should suspect either that some complication has developed or that the original diagnosis was in error and that the pneumonia may be of other cause—perhaps a different bacterium perhaps a virus or there may be an obstructing bronchial lesion or even pulmonary infarction

Anoxia Although many of the symptoms of pneumonia are due to overwhelming sepsis the factor of diminished pulmonary function must also be considered This factor is most important in old people or in persons with emphysema or in other circumstances where either the respiratory or the circulatory systems are handicapped by disease or deformity Not only does the patient with extensive pneumonia have a reduced ability to pump air in and out of the lungs but also a considerable portion of the pulmonary circulation may be directed to functionless segments of lung Cyanosis is a definite indication for oxygen therapy but it is not always detected easily especially in patients who are anemic or in patients in circulatory collapse with poor circulation in the skin Oxygen therapy a physiologic form of treatment not difficult to administer should be used more frequently than it is in this day when so much dependence is placed upon antibacterial drug therapy In addition to cyanosis oxygen therapy should be used in many patients where the only indication may be an exceedingly rapid cardiac rate where there are signs of circulatory collapse and whenever there is even faint suspicion of impending pulmonary edema *

The preferable method of treatment with oxygen is to utilize an efficient oxygen mask such as the BLB mask which is available in nearly all cities The nasal catheter is a simple and readily available means of supplying oxygen and can be improvised on short notice in cases of emergency The oxygen supplied need not be of medicinal type and can be obtained from some garage or machine shop in an emergency The oxygen tent does not supply oxygen in as high a concentration as can be supplied by the BLB mask but some patients prefer the tent and this method may be preferable when the patient is being treated under hospital conditions with private nursing care It is rarely as practical a method when patients are being treated in the home

Circulatory Failure As stated in the preceding section, circulatory failure is frequently a manifestation of unrecognized and decompensated respiratory failure with serious and potentially fatal anoxia The development of a rapid pulse with low blood pressure and symptoms resembling those of shock are serious danger signals when they occur during the course of pneumonia especially in older persons or in others known to have cardiac disease Treatment with small doses of epinephrin 0 5 cc of a 1 1000 solution every fifteen minutes for four or five doses may be helpful The use of caffeine is a time honored remedy but it should not be administered unless clear cut improvement follows the first trial dose or two Digitalis should not be employed unless there is *convincing* evidence of cardiac failure and then it may be given as in any other cardiac emergency

Good nursing care judicious use of mild sedatives avoidance of abdominal distention and constant supervision by an alert medical staff may greatly lessen the discomfort and seriousness of an extensive pneumonia even when conditions at first appear to be very grave

* See also Chapter 10

istically a progressive disease and abscess formation perforation, and peritonitis must be considered at all times as possible early complications Whether cholecystectomy or simple drainage of the gallbladder should be undertaken is a matter of surgical judgment to be determined by the local and general circumstances in the individual case

In most cases in which treatment has been instituted early, the acute condition will subside sufficiently in three or four days to permit cholecystectomy If cholecystectomy is required in an acute case, subsequent removal of the gallbladder should always be seriously considered especially if stones were present Occasionally, patients enjoy good health for many years following removal of stones and a simple drainage operation

CHRONIC CHOLECYSTITIS, CHOLELITHIASIS

Chronic cholecystitis is perhaps the most common organic cause of upper abdominal symptoms Treatment is likely to be complicated unless each case is diligently and conscientiously studied Misfortunes from delayed or omitted surgery will be spared many patients when diagnosis becomes more accurate and the indications for operation better defined As in other chronic diseases general rules do not apply for surgical intervention in cases of chronic cholecystitis

The question that immediately arises with chronic cholecystitis is whether stones are present or not On the answer may depend the choice of medical or surgical treatment An appraisal of the history including the family history in reference to gallstones of the physical findings and of the results derived from cholecystographic study and biliary drainage will be required if a precise diagnosis is to be made

Normal function as shown by roentgenography does not always mean the gallbladder is normal, nor does a poorly functioning gallbladder, so-called because of poor visualization or delayed emptying always mean that the gallbladder is diseased However, absence of a gallbladder shadow, if the patient retains the dye, does indicate that gallbladder function is impaired and that stones may be expected in most cases, but they may be difficult or impossible to demonstrate Diagnosis of chronic cholecystitis or gallstones based solely on cholecystography must be regarded as subject to error and should not be depended upon to the exclusion of other diagnostic data

Transduodenal biliary drainage may be of considerable assistance in the diagnosis of gallstones Of chief value is the finding of calcium bilirubinate pigment or cholesterin crystals in the bile which generally indicates that stones are present

Treatment

The treatment of chronic cholecystitis without stones is invariably medical On the other hand, once the diagnosis of cholelithiasis has been made, it is generally accepted that the gallbladder should be removed The exceptions to this, however, are not always easy to determine Cholecystectomy may be hard to accept if the patient complains of nothing more than flatulence Serious cardiac, vascular or renal disease as well as advanced age may present a prohibitive risk These are factors that must be weighed carefully, as the results of ill advised medical or surgical treatment may prove disastrous Gallstones may remain quiescent, as is attested by their discovery at autopsy in many cases after death from unrelated causes The difficulty lies in determining when they are quiescent

It may be argued that patients in whom gallstones are found accidentally who are not suffering from indigestion discomfort or pain in the upper abdomen and who

Cholecystitis

ACUTE

When the diagnosis of acute cholecystitis has been made the patient should be confined to bed at once preferably in the hospital and surgical consultation requested Nothing by mouth is advised for twenty four to forty eight hours depending on the severity of the attack Anxiety and pain which may be very severe can be relieved by giving 0 12 Gm of *sodium phenobarbital* hypodermically or demerol (50 to 100 mg) morphine (15 mg) dilaudid (2 mg) or pantopon (20 mg) may be given subcutaneously combined with atropine sulfate (0 6 mg) and repeated at four hour intervals if necessary Should any of these hypodermic preparations be poorly tolerated or cause aggravation of nausea and vomiting a rectal suppository containing 60 mg of opium with 15 30 mg extract of belladonna may be used A nitroglycerin tablet (0 6 mg) dissolved under the tongue at half hour intervals may be helpful at times or for immediate effect inhalations of amyl nitrite may be used Nitroglycerin and amyl nitrite are preferred to morphine by some because they relax the smooth muscle of the papilla of Vater which morphine constricts Recently *depropanex* a deproteinated extract of pancreatic tissue has been reported useful because of its spasmolytic properties in relieving pain due to colic 3 to 5 cc being given intramuscularly

An ice bag should be applied to the upper abdomen unless heat is preferred by the patient in which case the electric pad hot compresses or an old fashioned flaxseed poultice may be used Occasional small pieces of cracked ice may be given to relieve dryness of the mouth and thirst Until all pain has ceased and nausea and vomiting have stopped infusions of protein hydrolysate and 5–10 per cent glucose in saline are administered intravenously (2000–5000 cc daily)

Unless the attack is unusually severe or complications are threatening the patient will be able to take a small amount of warm liquid nourishment within twenty four to seventy two hours Very gradually cooked cereals junket gelatin diluted fruit juices and strained stewed fruits may be added to the diet Too generous feedings even though the patient may have a desire for more food are quite apt to stir up a subsiding cholecystitis and resumption of a full diet requires careful consideration For the same reason medicine that stimulates bile flow such as the bile salts and various proprietary preparations should not be given If surgery is deferred appropriate studies to determine the cause of the attack may be undertaken when the patient has convalesced fully Usually gall stones will be found

In one who has had suspected biliary colic or acute cholecystitis it is unwise to perform a transduodenal biliary drainage If stones should be present colic may be induced and perforation of the gallbladder or obstruction of one of the ducts may result Cholecystography is always indicated in the absence of jaundice but as it is necessary to defer it in the presence of acute or subacute disease a roentgenogram of the gallbladder and pancreatic area may be made In some cases this will reveal the presence of stones

If an acute attack of cholecystitis does not show definite signs of subsiding within forty-eight hours as indicated by reduction of the temperature sedimentation rate leukocyte count pain tenderness and muscle spasm operation should not be deferred Acute cholecystitis is character

least one half hour before breakfast will be found helpful, or a teaspoonful of equal parts of sodium sulfate, sodium phosphate, and sodium bicarbonate may act better, the dosage regulated so that purgation does not occur

In most patients antispasmodics and mild sedatives are helpful Tincture of belladonna (0 6 cc) or homatropine methyl bromide (5 mg)—preferably combined with phenobarbital (15 mg)—may be taken before each meal For flatulence and distention after meals an alkaline powder consisting of 0 6 Gm sodium bicarbonate, 0 6 Gm calcium carbonate, 0 3 Gm heavy oxide of magnesia, 0 12 Gm activated charcoal, and 06 cc oil of peppermint will provide relief Such a powder, especially with a little added sedative such as 0 1 Gm phenobarbital, taken at bedtime, will provide a more restful night Bile salts (0 2-0 4 Gm) in capsule or tablet form taken with each meal, are definitely indicated if only at periodic intervals (one or two weeks each month)

The sulfonamides, antibiotics, 'urotropine, salicylates, and various other remedies recommended from time to time in the treatment of chronic gallbladder disease, have been largely abandoned

Cirrhosis of the Liver

NO DEPENDABLE clinical or laboratory evidence exists on which a sound diagnosis of early cirrhosis can be established nor can the results of treatment be ascertained except in the latter stages of the disease Many glib statements are made concerning the effects of various remedies and means of treatment in the early compensated stages of cirrhosis, but even a cursory analysis reveals that the need for the treatment and the proof of its effects are both wanting

Boyd is probably correct in saying that 'the great majority of cases of cirrhosis can be divided into two great groups portal cirrhosis and biliary cirrhosis Until comparatively recent years the terms alcoholic cirrhosis and portal cirrhosis were used synonymously Recent studies, however have made it clear that influences other than alcohol play the decisive role At the moment the generally accepted theory is that nutritional deficiencies cause portal cirrhosis and current therapy is based on this premise The investigations of Connor, Patek, Gyorgy, Jolliffe, and others have been instrumental in developing such a theory However, the intriguing observations based on studies in nutrition—especially those of an experimental type—do not provide the whole answer to this problem Influences exerted by disturbances of the circulation, bacteria, endogenous and exogenous toxic agents, and a number of other factors remain to be determined It should be recognized that the term cirrhosis describes a terminal condition which is common to a number of primary etiologic factors

TREATMENT

Every effort should be made to remove any irritant to the liver such as alcohol carbon tetrachloride lead arsenic, gold compounds, mercurials and the sulfonamides also to eliminate intestinal parasites dysentery infections and to correct constipation, gallbladder disease cardiac failure, or any other systemic disorder likely to disturb liver function

Diet

The principles underlying the dietetic management of liver disease may be briefly

have not had colic or jaundice, should not be subjected to a major abdominal opera tion On the other hand, when any of the symptoms mentioned are present, the pa tient should be made to understand clearly that not having an operation may be more hazardous than having it One must also consider the risk, though it is relatively small, that stones may favor development of cancer of the gallbladder Practically all cancers of the gallbladder are associated with stones Such reflex disturbances as car diac arrhythmias rheumatic manifestations, migraine, and metabolic disturbances and even asthma may be caused by a diseased gallbladder When any of these conditions are found associated with gallstones, they favor the decision to operate

If cholecystectomy is not indicated, a regimen that will prove helpful most of the time can be devised to suit the individual patient

Diet Not much is known about the effect of diet in the treatment of chole cystitis but there are certain precautions that should be observed * First, some con fusion exists concerning the place of fat in the diet *If the patient is not overweight* a reasonable amount of fat may do no harm and actually may be beneficial Fat stimu lates emptying the gallbladder, which is desirable in the ordinary chronic type of disease Years ago 15 cc of olive oil was given before one or more meals and there is no good reason for not doing the same thing today, though it is now recognized that this does not eliminate gallstones For a few patients with severe metabolic derangement and hypercholesterolemia, a low fat diet containing a minimum of cholesterol may be indicated A fat free diet is almost impossible and would prove so entirely unpalatable that the patient could not be blamed for refusing it, an excess of fat is not desirable as it will disturb diges tion Some fat with each meal, but not too much with any one meal, is a good rule to follow

For example, a patient wishing an oyster stew and ice cream for luncheon will fare better if he takes no butter in the stew and omits the ice cream Dairy fats (butter, cream) and vegetable fats such as olive oil, are better tolerated than animal fats The patient should trim the fat from his meat, and avoid such meats as veal and pork and such fish as shad and mackerel, smoked fish and meat should not be per mitted Rich soups, oily salad dressings, gravies, stews rich sauces, condiments, pastry, and rich desserts must be avoided Coffee will be better tolerated without cream or sugar Chocolate and cocoa are never advisable Of the vegetables, cabbage, sauerkraut, and Brussels sprouts seem to give the most trouble, and dried beans sweet potatoes and other flatulent vege-tables are also discomforting

In general, lean meat including beef and lamb, and baked or boiled fish, poultry, eggs moderately, green vegetables stewed fruits, citrus fruits and other raw fruits cereals and potatoes (if the patient's weight permits), and plain desserts afford a very satisfying diet Patients should be cautioned to rest before eating if fatigued to eat leisurely, resist second helpings and avoid cold drinks, especially on an empty stom ach They also should be advised that losing the temper or becoming excessively agitated will invite trouble, that gluttony and alcoholic excess can cause biliary colic or pancreatitis, and that inordinate strain and tension will be reflected in a spastic biliary tract These are fundamentals of behavior in the life of the gallbladder pa tient that cannot be ignored

Drugs Drugs have a definite place in the treatment of gallbladder disease At least once a week, or perhaps every day for a week or two a mild saline aperient such as sodium phosphate (one teaspoonful in a glass of hot water) taken in the morning at

* See also Chapter 32

honey, jams and hard candy Milk—especially skimmed milk—used in abundance eggs used moderately, and butter used sparingly provide all the fats necessary to make the diet palatable and adequate Care should be taken to keep the diet low in salt (1 Gm daily)

Medication

Use of lipotropic agents (choline, methionine cystine lipocaic) is controversial *Theoretically if they have any use at all* it should be in those patients with large, fatty livers Once the fat has left the liver, as it always has in the scarred atrophic decompensated stage of cirrhosis no indication for any lipotropic substance exists Prior to this stage however and especially *if difficulties with a suitable diet are encountered*, choline may be given (0 5 to 2 Gm by mouth three times a day)

There is usually a need for some well tried drugs in any case of cirrhosis Fortunate is the patient whose physician does not become so involved in vitamin therapy, lipotropic substances etc that he fails to recognize the value of ferrous carbonate nux vomica tincture of gentian and cardamom compounds mild aperients and numerous other reliable remedies for flatulence, a jaded appetite and anemia Bile salts and pancreatic substances may be found helpful at times in improving the appetite and digestion

Complications

The complications of cirrhosis partially amenable to medical management are ascites jaundice and hemorrhage Ascites which eventually occurs in most patients if they live long enough ordinarily does not become demonstrable until the liver is badly scarred which leads in turn to ob*struction* of the portal circulation Although this appears to be an irremediable situation in some cases ascites seems to diminish when bed rest and specific dietetic therapy are initiated The necessity of bed rest for the patient with cirrhosis is not appreciated nearly as much as it should be It appears to contribute more to the alle*viation of symptoms* and the diminution of ascites than any other means of therapy Ascites that does not diminish after a few weeks of dieting vitamin therapy, and bed rest may require repeated paracentesis* Mercurial diuretics are frequently used to reduce ascites (2 cc twice weekly) but *they should not be used excessively* Ammonium chloride in large doses (4–6 Gm daily) may be tried but may ruin the appetite and digestion Consistent sustained benefit should not be expected from injections and other measures designed to force fluid output Effort may be spent better *in hastening rehabilitation of the* liver and its circulation by enforcing complete bed rest and by restricting the fluid intake (1200–1500 cc. in twenty four hours) or by using the Karell diet (1000 cc. of milk in twenty four hours in five feedings of 200 cc each) for a few days each week The salt intake should be restricted during such periods of fluid restriction

Surgical procedures designed to eliminate ascites have not proved successful At best they can only be palliative for a short time and seem hardly worth the risks involved They might be helpful for certain patients with recurrent hemorrhages from *esophageal varices*

Jaundice is a fairly frequent complication of cirrhosis occurring in a mild form in 70 per cent of cases No specific treatment other than that outlined for cirrhosis is necessary Fortunately, pruritus is much less troublesome than in the jaundice due to gallstone or carcinoma of the *pancreas* and may be relieved by intravenous injection of 0 1 per cent procaine in glucose solution

Hemorrhage from esophageal varices is managed in the same way as massive hem

* See also Chapter 49

summarized as follows (1) High protein intake promotes regeneration of normal liver tissues supplies amino acids which help restore serum protein depletion and exerts some lipotropic action thereby relieving the liver of some of the excess fat it has accumulated (2) High carbohydrate intake supplies a rich reservoir of glycogen in the liver protects it from injury by toxic agents and provides additional calories required for tissue regeneration and energy needs (3) Low fat intake is recommended because an excess of fat in the diet promotes fatty infiltration of the liver It should be remembered that too rigid an exclusion of fat is neither desirable nor beneficial because it makes meals unpalatable and deprives the body of certain fatty acids and fat soluble vitamins

Vitamins are included because vitamin B complex appears essential in protecting the liver and assisting in its regeneration vitamins A and D are deficient in liver disease largely because of diminished fat absorption the latter in part being the result of an insufficient excretion of bile diminished absorption of vitamin K may be expected to occur in the presence of jaundice associated with a decrease in prothrombin which favors hemorrhage

However care must be taken not to overdo vitamin therapy There is no evidence except some suggestive animal studies that a diet designed for the patient with cirrhosis does not contain all the vitamins his liver requires Although the appetite tends to wane in the patient with progressive disease of the liver he probably will ingest what he needs if the food is well selected and properly prepared It is natural that more thought will be given to meals if less attention is centered on vitamins If sufficient nourishment is not taken because of anorexia or distress after meals vitamin B complex may be given as brewer s yeast preferably in powdered or granular form One heaping teaspoonful stirred into tomato juice twice daily with meals should be sufficient If yeast is rejected one of the many fortified combinations of B complex in capsule or tablet form or in solution if preferred, may be given with one or more meals If the need is sufficiently great intramuscular injections of crude liver extract combined with the B complex and with vitamin C if desired will be found advantageous Rarely does the occasion demand the use by intravenous injections of large doses of vitamin B complex as has been recommended Wernicke s syndrome which is seen in the late stages of cirrhosis and is presumably due to a B complex deficiency will provide such an occasion Vitamins A and D are not required in large doses and can definitely impair an already feeble appetite and tottering digestion When vitamin B therapy is required the whole complex rather than individual fractions of it had better be given Vitamin K will be needed by those patients with low prothrombin values once or twice daily (menadione sodium bisulfite 10 mg intramuscularly or intravenously)

The daily dietary needs of the average patient may be met by 150 to 200 Gm of protein 300 to 400 Gm of carbohydrate and 100 to 150 Gm of fat To insure the ingestion each day of about 3000 calories of a diet so proportioned it should be taken in five to six feedings and at intervals of about three hours The protein may be supplied by lean well cooked meats fish and poultry balanced by generous amounts of dairy products and vegetables rich in protein Cottage cheese skimmed milk gelatin and similar foods are all desirable and if necessary may be supplemented by the various protein hydrolysates or amino acid preparations these generally are not very palatable The high carbohydrate content of the diet is furnished by cereals potatoes rice green vegetables stewed canned and fresh fruits whole wheat bread plain cake and puddings syrup

time each day, preferably after breakfast One or two glasses of hot or cold water containing the juice of a lemon or a pinch of sodium bicarbonate, if the patient feels better about having something in it should be taken on rising at least one half hour before breakfast In some troublesome cases a tablespoonful of an emulsion of agar agar kaolin or milk of magnesia with mineral oil may be required each night on retiring especially for the obese person, a teaspoonful of sodium phosphate in one half glass of water each morning one half hour before breakfast may be found effective For a short time, a simple saline enema (one teaspoonful of salt to a pint of warm water) or a glycerine suppository may be used in the morning These are not strongly recommended, however For those who are accustomed to smoking the morning cigar or cigarette after breakfast may serve a useful purpose

The act of defecation is one in which numerous influences play a part It is an act in which proficiency can be attained by the exercise of patience and the observance of a few practical rules First one should sit in a squatting position on a warm comfortable toilet seat and then concentrate on the business at hand Folding the arms across the upper part of the thighs and pressing on the lower abdomen will be helpful Perhaps some day toilet seats will be constructed so that one can assume a natural squatting position which will secure the benefit of apposition of the thighs upon the abdomen—a position which nature undoubtedly intended Defecation should then commence and be carried through in a leisurely manner If successful defecation does not come easily, which is usually the case, the routine described should not vary If a desire to defecate appears at any time during the day, the patient should be enjoined to comply with it at once

Meals should be eaten regularly and leisurely and be varied and well rounded Stewed or fresh fruit and at least two or three green vegetables should be included in the daily diet Prunes for breakfast with plenty of juice and not too much sugar, are sometimes very helpful An excess of roughage or bulk producing substances is neither necessary nor desirable For a while, small amounts of granular agar agar, or one of the proprietary bulk producers may be taken with breakfast or in the evening but not in the usual, excessive doses recommended by the manufacturers One or two heaping teaspoonfuls, stirred up in some water or mixed with cereal, is all that should be required Otherwise impaction may occur, especially in elderly persons Bran is not recommended

Colonic irrigations serve a useful purpose if they are given carefully and not too frequently An irrigation once a week, as a temporary measure can do no harm and frequently provides a great deal of relief However, dependence on them should be avoided

In these days of tense, hurried living the colon as well as other organs, reflects the character and habits of the individual one should not overlook the effect sedatives may be having in contributing to constipation

Diarrhea

DIARRHEA may be acute, recurrent, or chronic It is important to know which type is present Diagnosis should be based on etiology

The ordinary isolated acute attack of diarrhea not due to any specific type of infection such as amebic or bacillary dysentery, or tuberculosis will run its course

orrhage from peptic ulcer Incidentally the differential diagnosis in a patient with profuse hemorrhage is at times exceedingly difficult Unless it is known that the patient had cirrhosis or peptic ulcer, for instance, detailed questioning of the family or of the patient, if his condition permits, will help in settling the matter Some surgical measures to control esophageal hemorrhage appear logical and promising but at the moment, are not recommended because their results are inconclusive Recently tamponade of the esophagus and the instillation of thrombin have been successfully used in controlling massive hemorrhage

Hepatic coma, a terminal complication, presents an ominous situation not unlike uremic coma Strenuous steps may be temporarily effective The intravenous injection of glucose solution (2000 cc. of a 10 per cent solution daily) large doses of vitamin B complex administered intramuscularly or intravenously (100 mg thiamin 400 mg nicotinamide, 100 mg riboflavin), transfusions of blood plasma and oxygen inhalation may bring about a temporary remission of the condition

The use of aureomycin in the treatment of cirrhosis and hepatic coma has been suggested Its rationale is subject to question The drug is expensive, possesses deleterious side effects, and should be further studied before it is extensively used

Constipation

CONSTIPATION may be defined as infrequent or incomplete evacuation of the bowel resulting in stools that are dry hard and difficult to pass In large measure it depends on habit and the amount and character of the food ingested

For reasons unknown, variations in the tone and motility of the intestines may occur with the result that in the same person, atony of one part of the bowel may co-exist with spasm in another Ordinarily when abdominal distress or pain occurs, spasm of the bowel predominates Elderly people are especially susceptible to an *atonic rectal type of constipation (dys*chezia) which frequently leads to impaction Because of these variations in the behavior of the bowel it is not practical to speak of spastic and atonic constipation and attempt to delineate individual types of treatment for each

Before one ventures to treat constipation at all organic disease locally or elsewhere, should be eliminated as a cause Hemorrhoids and anal fissure tumors of the rectum or colon anomalies of the colon, pelvic tumors adhesions weakness of the abdominal wall as a result of pregnancy, illness, malnutrition or age, hypothyroidism, and such possible reflex causes as gallbladder disease *should all be considered before* assuming that constipation is purely of a functional nature

Deliberate negligence of the defecation reflex often begins in childhood and from then on the normal desire diminishes so that eventually an abnormal one must be created by the use of laxatives and other *unnatural devices When one considers the* number of bed ridden patients with chronic illness who continue to have normal eliminations, provided they always had observed strict regularity previous to their illness it becomes clear that such things as diet and exercise should not be overemphasized in the treatment of the constipated colon

The first step is an uncompromising determination to move the bowels at a fixed

and extent of the disease Thus, as far as the symptoms are concerned, diarrhea from tuberculous enterocolitis will not differ materially from that caused by amebic or bacillary dysentery Fortunately, specific remedies are available for the treatment of these particular intestinal diseases

Occasionally in a hypertensive individual, a bout of abdominal pain and diarrhea forecasts a cerebral vascular catastrophe

TUBERCULOSIS

Tuberculosis of the ulcerative type is one of the commonest diseases of this group It is invariably secondary to ulcerative *tuberculosis of the lungs, in fact, it is* axiomatic that no intestinal ulceration can exist without pulmonary ulceration Therefore examination of the lungs is imperative in order to determine whether the diarrhea is caused by intestinal tuberculosis

The ileocecal area of the intestines is the part *first and most often involved* The diagnosis is further established on the basis of the history, roentgen ray examination of the intestines by means of the barium meal, barium or contrast enema, and the presence of tubercle bacilli in the sputum, gastric washings, or stools Tubercle bacilli in the *stools, however, do not necessarily mean* the disease has affected the bowel

Streptomycin and *p* aminosalicylic acid (PAS) are immediately indicated once the diagnosis is made The clinical results of streptomycin and PAS therapy in tuberculous enteritis have been described as "dramatic , time will tell how lasting these benefits are *

Although tubercle bacilli may become resistant to streptomycin used in minimal tuberculosis, *thus rendering it useless at* some subsequent time, hesitancy in its use is scarcely warranted in the presence of ulcerative disease of the intestines This is a complication of advanced pulmonary disease in the great majority of cases In some cases the intestinal disease appears to heal while the pulmonary disease continues to progress There is less intestinal tuberculosis than formerly, though this is probably not entirely attributable to the use of streptomycin and PAS Better general care, more attention to nutritional requirements and especially earlier collapse therapy all contribute to healing the pulmonary lesion and reducing the incidence of secondary intestinal disease

Severe tuberculous diarrhea is sometimes relieved by 5 cc of a 10 per cent solution of calcium gluconate given intravenously daily or as the case requires, also, calcium gluconate or tribasic calcium phosphate may be given orally The former is preferable as it can be given as palatable 1 Gm tablets, two or three of which are chewed and swallowed with ample water after each meal

*AMEBIASIS**

In the majority of cases of amebiasis no diarrhea is present, in fact, many people harbor *Entameba histolytica* without having any acute symptoms Others may suffer only a mild type of colitis, and a third group experiences varying degrees of diarrhea, often of a violent type associated with blood and mucus in the stools, nausea, weakness, increasing prostration, fever, and leukocytosis Diagnosis is established by finding *Entameba histolytica* in the stools Amebic dysentery may recur at irregular intervals, at times after a period of years, during which the patient may become the victim of a chronic debilitating type of colitis

The patient may be ambulatory during *treatment for the subacute* and chronic phases of amebiasis, but he should be kept on a strict diet completely excluding alcohol, and he should avoid getting chilled or fatigued Amebiasis cannot be considered as cured until the stools on three consec

* See also Chapter 16

* See also Chapter 9

in a few hours or days Therapy will include bed rest and restriction of diet in order to give rest to both body and bowel The patient should eat or drink nothing except water as desired until he is somewhat relieved. Then he may have a cup of hot tea with a little sugar, some broth rice, barley gruel or cooked cereal with a little milk and sugar, milk toast, and gelatin, all in small amounts and at not too frequent intervals Laxatives or enemas serve only to aggravate discomfort The cramps which are invariably present will be relieved by hot stupes, heating pad poultices or a hot water bottle At first medication given orally may be vomited and as hypodermic injections are rarely necessary for a simple attack of diarrhea one can wait until nausea and vomiting cease and then give 30 mg of codein by mouth every few hours

Prompt relief of the diarrhea will usually be afforded by giving one or two ounces of a suspension of colloidal kaolin combined with pectin every two or three hours One teaspoonful of paregoric (camphorated opium tincture) and one tablespoon of compound chalk mixture may be given together in a little water every hour or two until the diarrhea subsides Bismuth subnitrate or subcarbonate 1 Gm, combined with paregoric 4 cc every three or four hours will be found more helpful in some patients As the diarrhea diminishes the diet may be increased cautiously and medication may be gradually reduced

Intermittent diarrhea except when due to some recurring emotional cause or indiscretion in eating and drinking and chronic diarrhea are usually of serious import Cancer of the colon especially the ascending portion should always be considered as a possible cause Other causes could be the various ulcerative diseases of the bowel (idiopathic ulcerative colitis amebic and bacillary dysentery tuberculosis regional enteritis and enterocolitis) enteric infections (Shigella group typhoid paratyphoid) food poisoning (staphylococcus), food allergies, toxic, metabolic, and circulatory disturbances (hyperthyroidism, cardiac failure, portal cirrhosis) chronic nephritis vitamin deficiency states (sprue, pellagra), psychoneurotic conditions, and unsuspected exogenous poisons (mercury, silver, arsenic)

The differential diagnosis of these conditions is outside the scope of this text However, some patients can be benefited only by specific types of therapy or by surgery One must study, perhaps repeatedly, the bowel discharges—grossly, microscopically, and by culture, sigmoidoscopic examinations should be made, and smears, cultures and biopsy taken from any suspected lesions roentgen ray examination of the colon, including if necessary double contrast enemas should be made Finally, barium meal progress studies and investigation of the gastric and pancreatic secretions are sometimes helpful Such an approach will almost certainly reveal whether the patient is suffering from cancer or from one of the specific or idiopathic types of ulcerative disease of the bowel or from a specific type of bowel infection The various systemic diseases vitamin deficiencies, allergies, and psychoneurotic and other conditions causing intermittent or chronic diarrhea will be suggested by the history and the objective evidence provided by physical examination and essential laboratory procedures

Pending the outcome of the patient's examinations the diarrhea regardless of cause, should be treated as any acute diarrhea The treatment of the more severe types of intermittent or chronic diarrhea, as observed in idiopathic ulcerative colitis and regional enteritis, will be discussed under the respective headings

The specific types of ulcerative disease of the bowel cause the same type of diarrhea as the so-called nonspecific or idiopathic types, *the character* and number of the stools and the amount of blood, mucus and pus depending largely on the severity

Diverticulosis or multiple diverticula of the intestinal tract are rather common They occur most frequently in the descending colon and sigmoid in persons past 50 years of age Treatment is unnecessary unless to relieve irritability of the colon and constipation which are often present and which may be factors in their production When diverticula become acutely inflamed, however, they present a rather characteristic picture which should be recognized before serious complications develop

Acute diverticulitis of the lower colon and sigmoid is quite apt to be mistaken for acute appendicitis carcinoma and diseases of the genitourinary tract or pelvis The usual symptoms are constipation which did not previously exist or has become worse occasional diarrhea, cramplike lower abdominal pain and tenderness (especially on the left side) fever, leukocytosis, rigidity and perhaps a palpable mass Symptoms that one may forget to attribute to diverticulitis are those pertaining to the bladder, such as frequency of urination and discomfort These are caused by inflammation or adhesions. Backache in the lumbosacral region, often present in colonic disturbances may be disabling and melena and frank bleeding may be observed Bleeding should not be attributed to diverticulitis, however, until carcinoma can be excluded Hemorrhoids, fissure, and polyps also are more likely to be the source of bleeding than diverticulitis Barium enema and sigmoidoscopic studies should be made in all cases in which diverticulitis is suspected

TREATMENT

The treatment of uncomplicated acute diverticulitis is medical The patient should be put to bed and have hot stupes or poultices an electric pad or a hot water bottle applied to the lower abdomen The diet should be liquid for two or three days Very gradually bland foods such as strained cooked cereals, broths, tea, custard gelatin junket, steamed rice, strained cream soups, milk toast, weak tea, postum, or weak coffee should be added

Antispasmodics and sedatives are indispensable Tincture of belladonna (0 5 cc) belladonna extract (8–15 mg), or atropine sulfate given every four hours, will prove helpful if well tolerated In most cases a mild dose of phenobarbital (15 mg) with the antispasmodic will be found desirable For those who do not tolerate belladonna homatropine methylbromide may be given combined with phenobarbital in tablet form every three or four hours An emulsion of kaolin and mineral oil may be given each morning on rising and at bedtime in 30 to 60 cc doses for an indefinite time

Management of the bowel in patients with diverticulitis will be found necessary for some weeks To prevent recurrence or acute exacerbation, nervous tension and fatigue are to be avoided, and the patient must permanently adhere to the regimen prescribed for irritable colon

Perforation and obstruction are the most serious complications of diverticulitis Perforation may occur into the bladder, leading one to believe that the original trouble is in the urinary tract Fistulas may produce an abscess On the first suspicion of abscess or perforation surgery is imperative Obstruction from diverticulitis may respond to medical management It is not always complete and colostomy or resection should not be performed until conservative measures have been given a chance, or unless malignancy is suspected Unfortunately one cannot always be certain of the *latter*, especially when study of a specimen obtained through the sigmoidoscope is not conclusive

utive days fail to show any *Entameba histolytica* As the disease is of a recurrent nature the stools should be checked at monthly intervals for six months

BACILLARY DYSENTERY*

Bacillary dysentery which is much more common than amebic dysentery is caused by *Bacillus dysenteriae* of which there are four main groups *Shiga Flexner Sonne* and *Schmitz* Considered species of the genus Shigella they are identified as *Shigella dysenteriae, S paradysenteriae S sonnei* and *S schmitzii*

Bacillary dysentery may be acute or chronic and of varying degrees of severity The diagnosis usually can be established by examination of the stools which contain a characteristic exudate Sigmoidoscopic examination frequently reveals a significant appearance of the mucous membrane cultures from which (or from the stools) will be positive during the first week or ten days of the disease Agglutination tests may be diagnostic if made between the first and third weeks

* See also Chapter 6

*Diverticulitis**

DIVERTICULA may be found in any part of the alimentary tract They are quite common in the esophagus duodenum and especially the distal colon they are found infrequently in the stomach The occasional diverticulum encountered in the terminal ileum is known as Meckel s diverticulum Multiple symptomless diverticula are designated as diverticulosis

Diverticulum of the esophagus may produce troublesome symptoms such as dysphagia regurgitation and foul breath An especially annoying symptom which occurs when the sac becomes large especially in old people is a constant spitting up of the overflow of the sac s contents a condition which becomes particularly annoying when the patient lies down In middle aged people in whom the sac has not become too large relief may be afforded by dilatation of the esophagus below the opening of the sac A diverticulum near the junction of the pharynx and esophagus may be removed surgically Not much can be done about large esophageal diverticula in old people whose age and condition make operation inadvisable

In most instances gastric and duodenal diverticula do not cause any particular symptoms and require no treatment However gastric diverticula have caused pain vomiting and hemorrhage and the more common diverticula may simulate ulcer and are often associated with varying degrees of duodenitis and irritable duodenum at times they are the site of peptic ulcer The treatment of diverticulitis of the stomach or duodenum is no different from that of ulcer If the symptoms cannot be attributed to anything else and if medical measures fail surgical removal or invagination of the diverticulum should be considered

Meckel s diverticulum found in the jejunum and lower end of the ileum may be the cause of strangulation intussusception or volvulus or may become inflamed and be mistaken for acute appendicitis Occasionally peptic ulcer may develop in a Meckel s diverticulum with resultant bleeding and perforation Any of these complications make operation necessary

* See also Chapter 42

amounts of cool water, cracked ice, champagne, ginger ale or hot strong tea with a little sugar may be acceptable In more extreme cases intravenous glucose and saline solutions will have to be used Complete bed rest and restriction of the diet to liquid and semiliquid bland foods for several days will be found desirable in most cases

CHRONIC

Internists, roentgenologists gastroscopists and pathologists are far from agreement on the subject of chronic gastritis Although the gastroscope has provided much information, changes observed in the mucous membrane of the stomach have not been correlated with any distinctive symptomatology, to make a clinical diagnosis of chronic gastritis possible Even less reliable are the roentgenologic findings Because of this lack of positive clinical signs the physician should be reluctant to diagnose the patient s illness as chronic gastritis and as with 'acute indigestion should conduct an unremitting search for trouble outside of the stomach

Surface irritation of the stomach mucosa resulting from alcohol and other irritants is one thing inflammatory processes in the submucosa and deeper layers, associated with secretory disturbances are quite another In the former condition symptoms resembling those of gastric ulcer may trouble the patient In the latter, disturbances of the circulation irritants and infections of the blood stream as well as nutritional deficiencies may contribute in producing chronic inflammatory changes Ordinarily the symptoms of chronic gastritis are anorexia morning vomiting of mucus (alcoholic gastritis) epigastric discomfort, and flatulence In older people, especially those with achylia diarrhea may be a troublesome symptom Chronic pancreatitis or lithiasis may have to be considered in the diagnosis and treatment of chronic gastritis

General Measures

If the condition is one of superficial irritation of the mucous membrane of the stomach relief may be expected to follow discontinuance of such irritating substances as alcohol, tobacco, highly seasoned dishes and excessively hot or cold drinks Various chemical irritants and drugs may also be the cause of chronic gastritis Gluttony and bolting of food are habits which should be corrected

When the inflammatory changes are chronic and involve the deeper layers of the stomach, the symptoms can be very troublesome and persistent Rest periods after meals especially after lunch, or even complete bed rest may be necessary Infected teeth or tonsils pyorrhea or chronic sinusitis may have something to do with chronic gastritis Such reasoning of course can only be presumptive but on general principles such focal infections should be eradicated A careful study will reveal that chronic gastritis is seldom an isolated phenomenon Associated diseases of the heart, blood vessels kidneys, and gallbladder, cirrhosis of the liver, and primary or iron-deficiency anemia are frequently present and must be treated if relief of gastritis is to be expected

Diet

In addition to the general measures careful dieting is essential Depending upon the severity of the condition the diet used for active peptic ulcer or, in milder cases that used for a healed quiescent ulcer may be employed * Ordinarily fairly conservative management is all that is necessary The patient should be instructed to eat lightly, never overloading the stomach The quantity as well as the kind of food eaten should never be disregarded If the patient gets hungry between meals he may

* See also Chapter 32

Gastritis

ACUTE

It is unfortunate that symptoms referable to the stomach frequently are indications of disease in other parts of the body Reflex gastric symptoms arising from disease elsewhere may strongly simulate actual intragastric disease For this reason the stomach is overlooked at times as a site of acute and chronic inflammation Even acute phlegmonous gastritis while not too common may escape detection

Although there is no clear cut syndrome by which acute gastritis can be recognized it is known to result from the ingestion of alcohol chemical irritants or poisons certain bacteria and thermal and mechanical irritants It is unlikely that this irritation is confined to the stomach alone and as in food poisoning some degree of enteritis probably occurs and the patient actually suffers from gastroenteritis with varying degrees of pain nausea vomiting and diarrhea hemorrhage and possible perforation also may occur The history usually discloses the cause of acute gastritis and special diagnostic procedures are not required unless it appears necessary to examine the vomitus stools or blood for poison or bacteria

Great caution must be used in distinguishing between acute gastritis and the many conditions which masquerade as acute indigestion Heroic attempts to wash out or empty the stomach by means of emetics may prove fatal to a patient suffering from a coronary thrombosis or cerebral embolism or cause additional misery to a person with gallstones renal colic or other abdominal and pelvic disorders that present the symptoms of acute indigestion Severe pain colic and fever do not occur in simple cases of acute gastritis and serious hemorrhage more often suggests ulcer of the stomach or esophageal varices Occasionally bleeding will occur when no demonstrable cause other than hemorrhagic gastritis can be found Acute infections (especially in children) brain tumors and emotional upsets are among the many conditions that must be considered in the differentiation between gastritis and acute indigestion

If poisoning has occurred the immediate need is to eliminate it and administer specific antidotes Discretion should be used in judging whether excessive vomiting and diarrhea have already so depleted the patient that measures to control them would not be more desirable than to augment them When the latter is necessary care must be taken in introducing the stomach tube especially in corrosive poisoning *

Most patients with acute gastritis are in great distress One is sometimes tempted to overtreat them and it is well to remember that at the height of the illness medication by mouth will aggravate their condition Pain is usually present and will require immediate attention It is well to inquire how the patient reacts to morphine or other narcotics in some these drugs cause nausea vomiting restlessness and excitement Dilaudid pantopon demerol or methadone are usually better tolerated and are more effective than morphine Sedation may provide some comfort When the patient can keep it down one of the milder liquid sedatives (phenobarbital elixir for example) may be given otherwise an intramuscular injection of one of the barbiturates (such as luminal sodium) may be necessary A mustard plaster applied to the epigastrium is helpful When nausea and vomiting have ceased small

* See also Chapter 50

Acute Hepatitis

ACUTE hepatitis may be of an infectious nature (acute catarrhal jaundice, acute infectious or infective hepatitis, epidemic jaundice, homologous serum jaundice), or it may be noninfectious (toxic hepatitis). Acute infectious hepatitis is presumably caused by a filterable virus which may be present in the blood for variable periods before clinical symptoms appear and which remains in the system long after the acute illness subsides. This latter fact should be remembered in the management of the disease. Acute infectious hepatitis or epidemic jaundice and homologous serum jaundice are probably variations of the same disease. There are, however, enough differences in their behavior to suggest that they may be caused by different types of viruses.

Acute infectious hepatitis may occur in sporadic or epidemic forms and is acquired through person-to-person contact or from the ingestion of infected food, water or milk. It is characteristically a disease of children and young adults. In most cases, jaundice is present in some degree but may not appear for a week or more after the onset of the illness. Prior to its appearance, the symptoms are suggestive of grippe.

Homologous serum jaundice does not appear to be spread by person-to-person contact, since the virus is not present in the feces or nasal secretions of infected persons. Ordinarily it seems to result from the administration of virus-infected convalescent serum or vaccines, transfusions of blood or plasma, and the use of improperly sterilized syringes and needles contaminated by blood of infected persons. The incubation period is considerably longer than that of acute infectious hepatitis, symptoms developing two to four months after the initial infection. The symptoms resemble those of acute infectious hepatitis. The pathologic picture of acute hepatitis is the same, whether it is of the infectious or serum type, varying from simple parenchymal degeneration to central or zonal necrosis of the lobules, or, in fulminating infections, to massive necrosis (acute yellow atrophy).

The diagnosis of acute hepatitis is based on the symptoms, chief of which are fever, anorexia, extreme malaise, headache, chilliness, nausea and vomiting, light colored stools, and an enlarged tender liver. As jaundice may not appear for five to seven days after onset, the diagnosis may be suspected on the basis of bromsulphalein retention, positive flocculation tests, and bilirubinuria. Leukopenia is also usually found. At the peak of the disease, which may continue for four to six weeks, the patient begins to feel better and within a week, though still deeply jaundiced, may feel quite well again. Jaundice that persists after six weeks indicates severe liver damage or a mistake in diagnosis. A careful restudy of the case should be made under such circumstances to rule out obstruction. Prolongation of the symptoms or persistence of the jaundice beyond six weeks, in the absence of obstruction, are causes for concern, as is a recurrence of the disease. Such developments suggest an error in diagnosis or may be indicative of residual inflammatory foci in the liver that may in some cases lead to a disabling progressive type of chronic hepatitis. The mortality rate is about 0.5 per cent.

Acute toxic hepatitis may be suspected when discovery is made that the patient has been given hepatotoxic drugs (cinchophen, arsenic, carbon tetrachloride, a chloroform). In other cases exposure to insecticides, certain cleaning agents, and

take a glass of milk and a few crackers or cookies The milk should always be sipped slowly and, preferably, warmed at bedtime Fruit juice, especially orange juice, is usually palatable but it will be tolerated more easily if diluted with hot water The patient can take a glass of orange juice, so diluted, on an empty stomach in the morning, but cold undiluted orange juice will prove disagreeable Cooked cereals eggs, vegetables (pureed if it seems desirable), meat, fish, and poultry (in small amounts and neither smoked nor salted) and plain desserts should make up the bulk of the diet Raw fruits raw vegetables salads, and especially salad dressings are usually not well tolerated Soups are quite unnecessary but a cup of cream soup or a puree may be allowed for variety Weak coffee or coffee substitutes without cream or sugar or tea, are acceptable beverages Smoking and the use of alcohol beverages, if indulged in at all, should be kept to a minimum Sometimes older people may use a light wine or a well-diluted though not too cold glass of whiskey without harmful effects

Medication

No routine medication can be suggested for chronic gastritis In those with achlorhydria, dilute hydrochloric acid seems helpful though an explanation for its efficacy is lacking Its taste is not pleasant but it may be made fairly palatable if given in doses of one half teaspoonful with two teaspoonsful of essence of pepsin or gastron' added to half a glass of water A dash or two of grenadine will flavor and give color to such a mixture The patient should be instructed to sip the dose through a glass tube during his meals If he objects to the mixture glutamic acid hydrochloride may be given in a capsule two or three capsules (0 6–0 9 Gm) being taken during each meal Pancreatin (0 5–1 Gm) and bile salts (ox bile extract, 0 3 Gm) *may be helpful in these* cases with associated cirrhosis and chronic disease of the biliary tract Various combinations of nux vomica, strychnine, tincture of gentian or cardamom compound rhubarb and soda mixture, and other stomachics serve their best purpose in chronic gastritis, this holds true also for those carminatives formerly used, such as peppermint, capsicum, cinnamon, and ginger

Gastric lavage each morning on arising helps some patients A solution of hydrogen peroxide (one teaspoonful per pint of water), isotonic solution of sodium chloride, sodium bicarbonate, or even silver nitrate in a weak solution may be used if such heroic treatment is needed at all Some individuals, even with an achlorhydria, derive satisfaction from a simple combination of antacid powders such as sodium bicarbonate, calcium carbonate, heavy oxide of magnesia, and bismuth subcarbonate or subnitrate taken after meals At times it may be desirable to add a small dose of a barbiturate and an antispasmodic (belladonna, hyoscyamus, homatropine methylbromide) to the powder, and always to add a drop or two of oil of peppermint, spearmint, or coriander to make the mixture palatable and more effective

Complications and Surgery

Chronic gastritis is usually associated with some type of anemia and vitamin deficiency Likewise, cirrhosis of the liver, cardiac failure, peptic ulcer, gallbladder, or other disease may be present—all of which require their own appropriate treatment Occasionally, one encounters a massive hemorrhage from chronic gastritis It should be treated conservatively, as would a massive hemorrhage from varices of the esophagus Surgery is not indicated in any type of chronic gastritis unless it is for an associated gastric lesion Subtotal gastrectomy hardly seems justified for the prevention of massive hemorrhage when no lesion can be demonstrated as the site of the hemorrhage

CONVALESCENCE

The patient should be carefully fed during convalescence, with the diet being supplemented by brewer's yeast in tablet or granular form Tincture of nux vomica and a palatable vitamin B elixir in a little water before meals may stimulate a jaded appetite A small dose of sodium sulfate or other simple saline or apéritif each morning on awakening (at least one half hour before breakfast) will be found helpful During this period caution should be exercised concerning too much activity, overeating, getting chilled and the use of alcoholic beverages Operative procedures should be avoided while jaundice is present unless definite indications for them exist occasionally liver biopsy for diagnostic purposes may be justified Lessening of the jaundice, subsidence of liver tenderness and reduction in the size of the liver are criteria of improvement Bed rest should continue to be enforced until such criteria are certain Resumption of activity must also be determined by improvement of appetite and digestion, increasing strength and disappearance of irritability and lethargy

PREVENTIVE MEASURES

The clinician is responsible for using all sanitary precautions relating to the disposition of the patient's stools, urine, and nasopharyngeal discharges Special attention should be given to needles and syringes that have been used during the patient's illness. It may be advisable to give 10 cc. of normal human gamma globulin intramuscularly and repeat the dose in one month to any exposed person This may confer a passive immunity for six weeks or more The exact value of gamma globulin however, in the prevention of hepatitis or infectious jaundice remains to be determined

It should be remembered that acute infectious hepatitis and homologous serum jaundice do not confer immunity against each other A patient with acute hepatitis should not serve as a blood donor for at least a year following his complete recovery if at all, and any one who may have occasion to give him injections or transfusions should know that he once had the disease Generally speaking it is good judgment to weigh the need for transfusions of blood and plasma very carefully in order to protect the patient from possible virus infection and this treacherous disease Clinical and laboratory evidence suggests that the present practice of plasma irradiation materially reduces the incidence of homologous serum hepatitis but does not guarantee complete safety.

Irritable Colon

JUST what an 'irritable 'unhappy, "unstable colon is, and particularly what manner of disease spastic colitis" and mucous colitis may be is purely conjectural It is easy to understand that a colon affected with extensive ulcerations with cancer or diverticulitis, or with any other inflammatory or infectious disease would be deranged and 'unhappy' One can also understand why a colon should become intensely irritable when a flood of foreign matter is suddenly projected into it especially from the wrong direction—a maneuver causing a reaction in the colon that could be designated when seen on a roentgenogram as view box colitis Differentiation of spastic colitis from ordinary constipation as it is seen in certain

toxic industrial chemicals or inhalants may give the clue to the diagnosis *

TREATMENT

The treatment of acute hepatitis is largely a matter of rest and diet Complete bed rest during the preicteric period and for several weeks afterward is most important Too early resumption of activities favors prolongation of the disease or a recurrence of its acute manifestations During the first week of the illness (the preicteric stage) only small liquid feedings at frequent intervals should be allowed As soon as possible the diet should be built up to 3000 calories daily, with high protein high-carbohydrate, and moderate fat foods protein, 150 Gm carbohydrate 400 Gm fat, 65 Gm An effort should be made to keep the fluid intake up to 3000 cc daily In order to maintain fluid intake and electrolyte balance intravenous injections of 5 per cent glucose in isotonic solution of sodium chloride may be necessary Protein and carbohydrate likewise may have to be administered intravenously (1000 cc of 5 per cent amigen in 5 per cent glucose solution) each day

Attempts should be made however to keep the protein intake adequate by oral feedings of amino acids and protein hydrolysate mixtures They are given in one tablespoonful amounts in milk or fruit juice three times a day Unfortunately these preparations are not too palatable and are apt to be refused Occasionally, feedings may have to be given by gastric intubation

Cracked ice and sips of ginger ale from a small glass of cracked ice are usually enjoyed Milk diluted with a little Vichy or Kalak water and sipped through a tube may be acceptable as well as orange juice diluted with some hot water Hot tea broths custards junket, fruit flavored gelatin and small amounts of cooked cereal may prove tempting during the first week later, a more general diet consisting of lean meats, chicken, fish one or two eggs daily, cereals, stewed or canned fruits, vegetables, plain puddings may be given Tea, coffee, milk and fruit juices may be used as desired

Vitamin B complex, which is necessary in maximal amounts (thiamin, 20 mg, riboflavin, 15 mg niacin 0 5 Gm) may be taken by mouth if well tolerated otherwise, it may be given parenterally Injections of vitamin K (5 mg daily) should be administered if the plasma prothrombin is less than 80 per cent Evidence of this will be seen in bleeding into the skin or mucosal surfaces in jaundiced patients The injections should be continued once or twice daily for several days If bleeding continues transfusion of whole blood will be required

During the first week, though severe pain is rarely present heat over the upper abdomen is comforting and may be provided by an electric pad hot water bottle or hot turkish towel compresses

Symptomatic medication is all that is required drugs are not indicated and may only disturb digestion Chemotherapy and antibiotics such as chloramphenicol have not been found effective Such lipotropic substances as choline or methionine are not recommended Sedatives are not well tolerated as bromides and barbiturates place additional burdens on the liver In any case there is rarely need for them for the illness itself sedates the patient quite enough. Itching is not apt to be troublesome in the jaundice of hepatitis as it is in those cases due to obstruction Treatment of pruritus by external means is usually unavailing Calamine solution containing 1 per cent phenol is helpful at times also worth trying is procaine 1 Gm in 0 1 per cent solution intravenously Aspirin may be used to relieve headaches and other pains

* See also Chapters 50 and 51

Gm) to be repeated in four to six hours if necessary The drastic use of penicillin and streptomycin is not usually necessary If the patient's course appears to be stormy, 300 000 units of penicillin may be given intramuscularly every twenty four hours

As these patients frequently suffer severe nausea and vomiting, they should be given nothing by mouth except a bit of cracked ice or small sips of water to allay thirst or dryness of the mouth Wangensteen suction to deflate the stomach and intestinal ileus and to keep the stomach empty of acid gastric juice which stimulates secretion of pancreatic juice, is usually required Intravenous saline combined with insulin, if hyperglycemia is present, and transfusions of whole blood or plasma (500 cc) will be required in combating shock and dehydration Glucose and insulin must be used carefully as diabetes is often present and sugar is known to stimulate secretion of *pancreatic juice In critical cases, paren*teral use of calcium may be necessary as the blood calcium may fall to very low levels, probably in proportion to the degree of fat necrosis present A careful check of the carbon dioxide combining power of the blood and of the blood urea and chlorides is important so that any deviation (acidosis, alkalosis azotemia) may be corrected

For about three days after the acute attack has subsided nothing should be given by mouth Feedings should then be resumed with caution or a recurrence of the attack will be invited The patient may have at first small amounts of warm liquid nourishment, including orange juice diluted with hot water every few hours to be followed in twenty four hours by such bland foods as junket, gelatin cooked cereals and boiled or steamed rice Full diet should be resumed very gradually Despite apparent recovery the patient should be observed carefully for a few weeks because abscess might develop which should be suspected if localized tenderness, fever, and leukocytosis appear

If the excessive pain, increased serum bilirubin, and jaundice of an acute attack do not show signs of subsiding within twelve to twenty four hours operation will be required to secure drainage of the infection and of the escaping pancreatic ferments Other indications for operation are evidences of spreading peritoneal irritation or of abscess formation Surgery, if possible, should be postponed during an acute attack since pancreatitis is so seldom an isolated phenomenon In many cases further study will disclose a diseased gallbladder containing stones, stones in the pancreas or its ducts, calcification or cyst of the pancreas, or persistent obstruction of the duodenum which will require operation A recurrence of acute attacks may be prevented by cautioning the patient to avoid overeating and excessive indulgence in alcohol

Chronic Relapsing Pancreatitis

In addition to an ordinary flatulent type of dyspepsia associated with epigastric tenderness, the symptoms pointing to chronic pancreatitis are attacks of upper abdominal pain, coming at long or short intervals The pain may be sharp, dull or cramplike, of any degree of severity, and may last hours or even days beginning in the epigastrium and radiating to the left or right side of the abdomen or into the back The repetition of acute attacks at increasingly frequent intervals is characteristic of chronic relapsing pancreatitis Nausea vomiting and occasionally jaundice accompany the pain Steatorrhea, creatorrhea an increase of the serum amylase and lipase and glycosuria may be found A diminution of the pancreatic enzymes in the duodenal contents may be observed accounting for the steatorrhea and creatorrhea Low values will be obtained in response to the secretin test in many pa

nervous people is difficult Occasionally under some unusual circumstances usually of an emotional order, a person may be inconvenienced by a sudden bout of diarrhea The colon in such people is governed by a hair trigger mechanism but it can hardly be called diseased, nor are the people necessarily unstable

For treatment of the irritable colon the same regimen is advised as for constipation Weight should be corrected sedatives and antispasmodics prescribed with discrimination and more rest advised for the weary and more serenity for the high strung

In general the most effective treatment for these patients is to divert their minds from their bowel movements to more salubrious pursuits For persons suffering from a genuine emotional disorder in which the colon has become involved the treatment of course should be for the emotional condition and not for the colon. This requires rest, appropriate exercise, occupational and physical therapy, and in extreme cases, psychiatric consultation *

* See also Chapter 25

Pancreatitis

ACUTE

The cause of acute pancreatitis is still a matter of controversy One opinion is that obstruction at or near the ampulla of Vater causes diversion of infected bile into the main pancreatic duct As a result the pancreatic secretions are forced back into the pancreas through the acinar cells and into the interstitial tissue This causes digestion of the tissue by the pancreatic enzymes which in turn leads to hemorrhage necrosis and suppuration The various types of acute pancreatitis such as interstitial hemorrhagic, necrotic and suppurative may be regarded as degrees of inflammation rather than different varieties of the disease

The diagnosis of pancreatitis should not be too difficult Unfortunately it is often not considered when an attack of epigastric pain seizes the patient The attack is frequently preceded by overindulgence in alcohol an unusually heavy meal or an emotional upheaval It should be suspected at once in a person suddenly seized with pain in the upper abdomen The pain may be excruciating and last hours or days frequently radiating to the left side and extending through to the back It may also radiate to the area of the gallbladder or directly across the upper abdomen Nausea and vomiting are at times extreme If the inflammation is extraordinarily severe shock and even death may occur within a short time In all suspected cases, the serum amylase and lipase values should be immediately determined as these are of unquestioned value in the diagnosis of acute pancreatitis normal values however do not exclude it

Treatment

Most cases of acute pancreatitis respond to conservative management. It is good judgment to defer operation during an acute attack which will usually subside and afford time for a more leisurely appraisal of the case The patient should be hospitalized in order to correct fluid and electrolyte imbalance and for close observation Demerol" (0 1 Gm), papaverine (60 mg) "dilaudid (1 9 mg) pantopon (20 mg) or morphine sulfate (15 mg) are required to secure relief of pain and anxiety Sedation should be assured by an injection of phenobarbital sodium (0 12

ities diet smoking and drinking will have to be observed for a long time—perhaps a lifetime—if healing of the ulcer is to be achieved and a recurrence prevented This mode of life will have to be followed even though he may submit to surgery He must be impressed with the necessity of avoiding emotions such as fits of anger or uncontrolled anxiety and the indulgences that arise from an undisciplined turbulent manner of living Vascular disturbances both functional and organic are being recognized more and more as important factors in the formation of an ulcer Also of significance are certain chemical deficiencies in the blood, such as protein and vitamin C

The treatment of uncomplicated ulcer is the same whether in the stomach or duodenum although the patient with a gastric *ulcer will have to be kept under closer ob*servation because of the possibility of cancer It is best to suspect that every gastric ulcer is malignant and to keep alive this suspicion by careful examinations of the lesion every month or so until healing has occurred These examinations should include a careful evaluation of symptoms physical examination blood count gastric analysis and stool examination for the appearance of blood Roentgenologic examination will usually be indicated and at times gastroscopic examination Surgery must be performed if there is any doubt about the character of the lesion or if it recurs after healing had apparently taken place

The management of a peptic ulcer will vary according to the age and personality of the patient duration of the disease and behavior of the ulcer Peptic ulcer may occur from infancy to old age—in the latter period it usually escapes detection It may be acute or chronic complicated by pyloric stenosis hemorrhage or threatened perforation Lastly the patient may be intractable or the ulcer unmanageable All of these factors make individualization of treatment imperative Probably the ulcer patient has suffered in the past from the effects of too rigid and prolonged dieting

Diet

Palatable, adequate meals must be provided or the patient will rebel and abandon treatment in disgust especially if feeling better * If symptoms are severe or have been recurring for a long time bed rest for two or three weeks is advantageous However if bed rest will occasion more worry and fretting it should not be insisted upon Large hot compresses applied to the entire abdomen for one hour two or three times daily, may be helpful in securing relaxation of a patient who is tense and nervous In the average case, the dietetic treatment should commence with hourly *feedings of milk and cream (15 cc of each)* every hour from 7 00 A M to 10 00 P M for one or two days Usually one or two feedings during the night will be required Should pain during the night become troublesome Sandweiss advises lavaging the stomach between 11 00 P M and midnight with a quart of hot water to which a teaspoonful or two of bicarbonate of soda has been added This is followed with one ounce of warm olive oil Winkelstein has suggested continuous milk drip through the night for certain recalcitrant cases

As the patient s condition improves the interval of feedings may be lengthened to two hours the amounts slowly increased and such foods as cooked cereals boiled rice, pureed vegetables eggs buttered toast and plain puddings gradually added to the *feedings Ordinarily within two or three* weeks the patient should be taking three regular meals each day (total amount of each not to exceed 400-500 cc) consisting of the foods previously mentioned with the addition of a little lean meat or fish chicken cooked or canned fruits cottage

* See also Chapter 32

tients The liver may be enlarged and loss of weight is quite evident A roentgenogram of the pancreatic area should be made to determine if stones or calcification of the pancreas are present The incidence of correct preoperative diagnosis of chronic pancreatitis is disquietingly low

Treatment

Treatment is mainly dietary Patients should not eat large meals and the diet should be of a high protein high-carbohydrate, and low fat content * Skimmed milk, cottage cheese, lean meat and fish, whole wheat bread, cereals, green vegetables citrus fruits and plain puddings or stewed fruits form the bulk of the diet Weak tea without cream and black coffee may be taken once daily Cocoa chocolate, and fats are not well tolerated One of the protein hydrolysates taken at meals in skimmed milk may be useful Large doses of pancreatin (2–4 Gm) in enteric coated tablets with meals are desirable until lessening of the steatorrhea and creatorrhea shows that stools are more normal Brewer s yeast (4 Gm) in powdered or tablet form with meals, and 2 cc of crude liver extract intramuscularly two or three times a week will be helpful Supplemental vitamin therapy —especially B-complex factor—is of value for those patients suffering from malnutrition The fat soluble vitamins are seldom well tolerated and may disturb digestion

Patients with pancreatitis should always be carefully studied for evidence of biliary tract disease

Surgery will be necessary in patients with chronic pancreatitis who suffer persistent or progressive jaundice or who may have the complications or associated conditions mentioned under acute pancreatitis A number of operations have been devised for acute and chronic pancreatitis Drainage of the lesser sac combined with cholecystotomy, partial and total pancreatectomy, pancreolithotomy, sympathectomy and vagotomy, sphincterectomy, and subtotal gastrectomy and splanchnicectomy are among the operations indicated, depending on the severity of the disease, the local findings and the general condition of the patient

* See also Chapter 32

Peptic Ulcer

PEPTIC ulcer must be thought of as a constitutional as well as a local disorder Attention would scarcely be limited to an ulcer of the toe in diabetes similarly, treatment of an ulcer of the stomach or duodenum requires management of the disease as a whole Although the cause of peptic ulcer is unknown there is little doubt that pylorospasm and hyperacidity contribute to its pathogenesis, they must be controlled if healing is to take place Medical or surgical treatment designed solely to correct hyperacidity is almost certain to fail It is possible that pylorospasm is more of a controlling influence in ulcer production and chronicity than is hyperacidity Fortunately, the ordinary medical measures designed to correct hyperacidity likewise relieve pylorospasm and thus ameliorate the patient s symptoms

TREATMENT

As patients with ulcer rarely experience a feeling of relaxation rest is the first thing they require At the outset, the patient should be told he has a disease that is amenable to treatment but that certain reasonable limitations regarding his activ

be continued for some weeks or months after all symptoms have subsided as the patient may be symptomatically well though the ulcer is not healed and acidity is high

Many substances recommended for ulcer, such as enterogastrone urogastrone anthelone duodenal extracts and cabbage juice, are of experimental interest only and have not demonstrated value in human studies Furthermore the remedies that have been advocated from time to time for controlling acidity, such as eugenol Kutrol,' methantheline bromide (banthine), and others too numerous to mention are not recommended at this time, though they have merit, because it is felt they do not possess sufficient advantages over the well established antacids, and antispasmodics and in the case of most, their high cost makes their use prohibitive

Despite his comfort which leads to belief that his ulcer has healed the patient must continue to submit with good grace to reasonable restrictions of his diet both as to character and amount, for an indefinite period if good health is to be maintained When attacks of emotional storms are encountered the wise patient will learn to return to his acute ulcer regime until harmony ensues

COMPLICATIONS

Little has been written about the prevention of the two most common and dangerous complications of ulcer hemorrhage and perforation yet they are preventable in most cases Hemorrhage will occur most often in persons with chronic ulcer who have not led the ulcer life' It is especially apt to occur from overloading the stomach from sudden severe anxiety, and from unusual physical effort such as heavy lifting Hemorrhage and perforation more often occur with the change in seasons in early spring and late fall and at such times the patient should be cautioned to take especially good care of himself

Hemorrhage

The potential behavior of massive hemorrhage from peptic ulcer cannot be predicted with any measure of confidence A situation gravely ominous at one moment may brighten up the next, or one that seems fairly well in hand may quickly become unmanageable In general, the older the patient the more concern must be felt for his safety While every precaution must be taken with younger patients fatalities among them are uncommon In fact massive hemorrhage itself in young people is infrequent, from 80 to 90 per cent of severe hemorrhages occur in those over 45 years of age

Hemorrhage usually occurs during the night The patient sometimes is awakened with a desire to defecate and suffers from nausea faintness and vomiting If the hemorrhage is severe he may vomit blood even though the ulcer is in the duodenum if the hemorrhage is sudden and profuse he may evacuate fresh clots of blood Frequently, the only indication that hemorrhage has taken place will be the appearance of black stools Any suggestion of hemorrhage calls for immediate and absolute bed rest If bleeding is profuse the patient will exhibit intense anxiety This should be controlled by a hypodermic injection of phenobarbital sodium or a narcotic (demerol dilaudid, or 'pantopon) Morphine, of course, may be used although the fact that it causes nausea and vomiting in some persons must be kept in mind

The patient should be kept warm Transfusions of whole blood (500 cc) should be given slowly at intervals of eight to twelve hours if the hematocrit reading is below 28 or the hemoglobin below 50 per cent, the red cell count below 3 000 000 the systolic blood pressure below 100 or the pulse above 120 Mortality from

cheese and most vegetables excepting cabbage, onions peppers cucumbers, stalks of cauliflower, broccoli, and other vegetables of a coarse variety Whole wheat bread and whole grain cooked cereals should be permissible by this time Fruit and vegetable juices to which are added a little hot water if not tolerated well when cold should be part of the daily menu At mid morning midafternoon and bedtime a glass of milk or malted milk (skimmed milk if the patient's weight is excessive) should be taken with a few plain soda or unsalted crackers At bedtime the drink should be warmed and sipped slowly

In many cases it will be found desirable to add to each glass of skimmed milk one or two tablespoonfuls of a proprietary protein vitamin mixture Because of dietary restriction a vitamin deficiency occurs in many ulcer patients and it is well to see that sufficient amounts of the B complex and C vitamins are taken daily In the presence of anemia iron and intramuscular injections of crude liver extract with or without the B complex given two to three times weekly will be found desirable Since most patients with uncomplicated ulcer are not anemic but rather polycythemic iron or other antianemic remedies are usually unnecessary * As soon as possible the patient should be placed on a full diet of about 3000 calories with adequate provision of all the essential nutriments

A word of caution about the dietetic treatment of ulcer is appropriate The patient with uncomplicated ulcer is undoubtedly undernourished from too many deprivations in his diet Undernourishment retards recovery of the individual as well as healing of the ulcer Free of stress and anxiety patients with ulcers can eat quite generously and normally without fear of distress For this reason temperamental rather than dietetic restrictions should receive primary consideration

* See also Chapter 14

MEDICATION

The most useful drugs in the treatment of peptic ulcer are the antispasmodics, sedatives and antacids If an idiosyncrasy does not exist tincture of belladonna is preferred using 1-2 cc. every four hours or before meals and at bedtime Dryness of the mouth and nose and visual disturbance may occur In such cases the dose of belladonna should be reduced Synthetic antispasmodics may be substituted and a barbiturate added for sedation if belladonna proves unsuitable Antispasmodics of the atropine type should not be given to patients with glaucoma

For neutralizing purposes one of the alkaline antacids such as calcium carbonate, sodium bicarbonate, heavy oxide of magnesium or bismuth subcarbonate may be utilized All may be used alone or combined in a single powder (0 6 Gm of each suiting the amount of bismuth or magnesium to the patient's bowel habits) and given one hour after meals and at bedtime Alkalosis may develop in some persons from the excessive use of alkaline antacid powders This should be suspected when the patient complains of headache, irritability loss of appetite weakness nausea and vomiting In the presence of such symptoms the powders should be stopped and appropriate therapy instituted If preferred one of the aluminum gel preparations (neutral antacids) may be given in 4 or 8 cc doses in a little water every four hours or one hour after each meal and at bedtime Protein hydrolysates have value as neutralizing agents and may be used for this purpose as well as nutrition The anion exchange resins and mucin have been helpful when more conventional methods fail but ordinarily possess no great virtues over the antacid powders Irradiation directed to the fundus of the stomach may reduce hyperacidity but is not recommended for routine purposes Antispasmodics antacids, and sedatives should

and followed with roentgenograms at weekly intervals If the total amount drained each day continues to exceed the amount of the feedings the obstruction requires operation

Marginal Ulcer

This unfortunate complication following resection or gastroenterostomy is more *easily prevented than cured It will be seen* much less often when the surgeon and the patient both realize that no operation confers immunity to future ulcers If these are to be prevented the patient will have to accept an antiulcer regimen as long as he lives The surgeon should not discharge an ulcer patient as cured as soon as he is able to leave the hospital, but should establish a definite schedule for future examinations

GASTRIC ULCER*

Many surgeons believe all gastric ulcers should be removed Certainly one cannot dispute removal of a gastric ulcer that resists healing or shows the slightest evidence of recurrence On the other hand benign ulcers of the stomach do occur and do heal Although the risk of making a mistake in diagnosis or deferring operation too long is very real such a mistake need be made but once to persuade the physician that surgery for all cases is proper

There appears to be no absolutely safe criteria for the diagnosis of an early lesion In the best hands *the diagnostic error is at* least 10 per cent If one is to play safe, healing must be demonstrated by roentgen ray or gastroscope or both within a few weeks' time Healing should be complete and permanent Likewise the patient should become symptom free epigastric discomfort should have disappeared, and he should display no sign of diminishing vitality, loss of weight loss of appetite or anemia In fact he should present unqualified local and general evidence of good health

Despite such reassuring criteria the physician should hesitate to treat a gastric ulcer medically in persons over 50 years of age with a short history, because of the danger of malignancy Such caution is especially necessary if the ulcer is on or near *the greater curvature Of the patients that* come to operation those who have been under treatment the shortest time (less than a month) have a decidedly better chance of survival In short reliable evidence shows that the majority of patients with gastric ulcer should be operated upon and may expect satisfactory results from gastric resection The physician who treats such patients medically is assuming a grave responsibility

Subtotal resection of the stomach is conspicuously satisfactory for gastric ulcer For the complicated duodenal ulcer, a completely successful operation has not yet been devised Despite its inadequacies subtotal resection is usually the choice The one drawback of the choice however, is the possible occurrence of marginal ulcer for this vagotomy may be an opiate but not a cure

The individual with the handicap of a difficult personality is an undesirable candidate *for any operation It is* unfortunate for all concerned if the state of his ulcer requires surgery—certainly his disposition will not be improved nor his capacity to accept disciplined living augmented Intrinsically he is hopeless and unless he must have surgery to save his life he is best treated by medical means

*See also Chapter 42

hemorrhage probably could be appreciably lowered if less hesitation were felt about the liberal use of transfusions During this period the urinary output should be recorded as a total of 1000 cc for twenty four hours is desirable

A bleeding ulcer is an active ulcer and for this reason immediate liberal feedings would not seem desirable for most patients Withholding all food by mouth for at least twenty four hours is therefore recommended and especially until all nausea and vomiting has ceased The immediate needs of the body can well be met by parenteral injections of glucose and saline plasma and whole blood gauged by repeated estimations of the blood urea chlorides carbon dioxide and the indicated chemical studies Although now seldom used a slow rectal drip might be helpful as considerable quantities of fluid may be given in this manner Within twenty four hours small feedings may be begun by mouth for example 30-60 cc of diluted milk malted milk strained gruel junket gelatin or cream soup may be given every hour (7 00 A M to 10 00 P M) If the blood pressure pulse hematocrit hemoglobin and the general condition indicate that bleeding has stopped the feedings may be doubled the second day and thereafter a conventional ulcer diet gradually resumed Simultaneously *medication* by mouth may be begun

Surgery* Whether surgery for massive hemorrhage should be undertaken is always difficult to decide No set of rules applies to all patients First of all diagnosis of ulcer should be certain since the hemorrhage may be from esophageal varices or gastritis While arteriosclerosis may occur in the young it is dangerous to temporize with bleeding beyond an age of 45 years because of the condition of the arteries Hemorrhage from ulcer especially if recurrent and not under complete control within twenty four hours or that develops while the patient is under treatment usually calls for surgery

*See also Chapter 42

Perforation

Perforation can occur in an ulcer that has been relatively quiescent and painless perforations may occur in patients who have undergone vagotomy or sympathectomy The condition calls for immediate surgery In operations performed within six hours after perforation with subsequent administration of penicillin and sulfadiazine the mortality rate approaches zero Early operation and chemotherapy reduce chances for such a complication as subphrenic abscess Temporizing with perforation by any nonsurgical means is inadvisable

Pyloric Obstruction

Obstruction occurs in gastric ulcer but is more often due to duodenal ulcer or gastric cancer Gastric ulcer coincident with pyloric obstruction usually requires immediate surgical intervention Even if palliative measures seem permissible they are best carried out in the hospital Continuous suction through a nasal tube may be employed for twenty four to forty-eight hours during which time parenteral fluids (glucose saline or water and amino acids) are administered Another effective treatment advocated by Wilkinson is alternate drainage and feeding through a nasal tube throughout the day Ninety cubic centimeters of milk or malted milk with vitamin and protein supplements added are given every hour For the following half hour the tube is clamped it is then allowed to drain for the next half hour This procedure is carried out from 7 00 A M to 10 00 P M with suction continuing through the night If the total amount drained each day becomes less than the amount given the plan is continued three or four days The patient then is placed on a strict regimen for active ulcer

Chronic Idiopathic Ulcerative Colitis

ULCERATIVE colitis may be acute or chronic. As one cannot be sure of the cause the term idiopathic (*unknown*) instead of nonspecific should be used. Idiopathic ulcerative colitis is probably due to more than one factor. Familial tendencies, disturbances of intestinal function (spasm and hypermotility), bacteria, nutritional deficiencies, allergy, and emotional disorders all appear to contribute. One cannot attribute to any of these factors a primary or even a major role. A large number of patients will enjoy long and even permanent remissions on conservative management. In fact, the patient may undergo a spontaneous remission or manage quite well by applying lessons learned from personal experience. Some patients will resist acute devastating attacks of the disease with supportive management alone. Others, despite the best of care, drift into a state of invalidism as a result of protracted, uncontrollable diarrhea, hemorrhage, starvation, and anemia. Some develop such general complications as arthritis and local complications such as intestinal polyps (*true and false, the former carrying a very definite threat of malignancy*), stricture, abscesses, perforation and perianal fistulas. In advanced cases it is reasonable to expect that some damage will be suffered by the liver, kidneys, heart, blood vessels and other organs. Invalidism and complications will suggest the need for surgery; in the former, operation will probably be a wise selection; *in the latter, there is no choice.*

This disease need occasion no despair. Patients who seemed to have reached a hopeless state often suddenly change for the better. Pregnancy has dramatically transformed an ailing, failing young woman to one blooming with health. Although its course is entirely unpredictable, there are enough pleasant and unexpected results, even in desperate cases, for the physician to persevere, be optimistic, and help the patient's morale by constantly reassuring him that all will be well.

GENERAL MANAGEMENT

The average patient with idiopathic ulcerative colitis does not require absolute bed rest or hospitalization. Many patients do better without such restrictions. For them one or two rest periods during the day are helpful, however, the patient with severe acute symptoms or in relapse should go to bed until the acute condition subsides. Above all else, patients should avoid getting fatigued or chilled, and should always keep their feet and body warm. In winter a woolen abdominal binder is comforting. Heat applied to the abdomen for one half hour periods by stupes, poultices or an electric pad once or twice a day, but especially at bedtime, provides relaxation and rest.

Emotional disorders have been stressed as a cause of this disease to such an extent that psychotherapy has been considered essential. However, the sympathy, interest, and personality of the physician will afford a kind of psychotherapy that may prove much more effective than that derived from analytic exploration of the patient's personality. This can be as injurious as meddlesome surgery. For some exceptional patients, the physician will find it good judgment to request the assistance of a psychiatrist.

DIETETIC TREATMENT

Diet is, of course, a matter of considerable importance for the patient with ten or twenty bloody stools a day, but patients should not be made unhappy and become

Regional Ileitis

REGIONAL ileitis is a disease of unknown etiology occurring predominantly in young adults between 20 and 30 years of age The diagnosis in established cases rests upon the history of intermittent diarrhea, low grade irregular fever a tender palpable mass fixed in the right lower abdomen, and the presence of fistulous tracts in the perianal region associated at times with perirectal abscess Characteristic roentgenologic findings are observed following a barium meal study

While the disease is called regional ileitis it may occur in other parts of the small intestines such as the jejunum and even the duodenum In certain cases repeated attacks occur in which isolated areas of the small intestines present a red swollen edematous appearance which may subside with no demonstrable after-effects At times especially when the attacks are accompanied by eosinophilia they would appear to be of an allergic nature

The treatment of early uncomplicated regional ileitis or enteritis is always medical and nonspecific Under such circumstances the outlook is frequently good The treatment is entirely symptomatic and supportive as outlined under the subject of diarrhea In the early cases a low residue diet eliminating any food to which the patient may be allergic rest fresh air and sunshine or ultraviolet therapy and such drugs as are indicated for sedation and the control of the diarrhea will prove quite satisfactory

MEDICATION

Chemotherapy in general has proved di appointing Succinylsulfathiazole, sulfa thalidine, and sulfaguanidine appea helpful at times in doses of 3–4 Gm eac day by mouth Of the antibiotics strepto mycin (2 Gm each day intramuscularly and chloramphenicol (eight 0 25 Gm cap sules each day) are of apparent temporar benefit in severely toxic patients The prob ability is that they possess no curative e fects and should be used only in carrying patient through a stormy period

SURGERY

When the disease has become so ad vanced that cicatricial stenosis and othe complications have developed, surger eventually becomes necessary The result from surgery will depend on the extent o involvement of the intestines and the pres ence or absence of internal and externa fistulas Whether resections or short-circuit ing operations as ileotransverse colostom with transection of the ileum well abov the diseased area should be done will de pend on the local findings and the genera condition of the patient * Recurrence ma be expected in 15 to 20 per cent of case after surgery and may occur as long as four teen years after operation In such cases the patient requires the same managemen as before operation

*See also Chapter 41

sert, plain cooked puddings, gelatin, junket, custard, and similar dishes are satisfying and nutritious As soon as possible the daily intake should contain 130–140 Gm protein and 3000–3500 calories

Vitamins are indispensable for most patients with ulcerative colitis because their loss of appetite, and frequent stools, to say nothing of blood loss, inevitably lead to varying degrees of malnutrition All of the vitamins, in doses indicated by the patient s condition, should be prescribed Especially important will be vitamins C and K and the B complex

MEDICATION

The therapeutic treatment of ulcerative colitis leaves much to be desired Many drugs, vaccines, serum sulfonamides, antibiotics, medicated irrigations of the rectum, and other procedures have been advised If vaccines are helpful and many *doubt that they are their use might best be* left to those with special training and laboratory facilities At one time or another, all the sulfonamide drugs have been tried especially those with a low degree of absorption in the intestinal tract, such as 'neoprontosil, sulfaguanidine, and succinylsulfathiazole The latest of these drugs is salazopyrin, a combination of salicylic acid and sulfapyridine, which Bargen states "may be considered a valuable adjunct in the treatment of ulcerative colitis

Caution must still be observed concerning the use of any of these drugs keeping in mind their possibly harmful influence *on the blood kidneys and even in the in*testinal tract Also, if they are to be given a fair trial, they should be used early in the course of the disease Penicillin streptomycin, aureomycin, and the newer antibiotics have not been demonstrated to exert any consistent benefit in this disease In an occasional case where a specific secondary infection is present, they may be helpful Penicillin (500 000–800,000 units daily) in the treatment of a desperately sick person might at times swing the pendulum the right way

Certain drugs seem essential for the treatment of ulcerative colitis, chief of these are the antispasmodics and sedatives, such as atropine sulphate, belladonna, homatropine *methylbromide, codeine and pheno*barbital or one of the many barbiturate compounds The antispasmodics mentioned are effective given alone or with phenobarbital, every four hours or before meals and at bedtime Codeine sulfate helps greatly in alleviating irritability of the colon when given after each meal (15–30 mg tablets) and at bedtime, if necessary Colloidal kaolin and bismuth should help more than they do in ulcerative colitis Although they prove disappointing at times, one or both of them may be given in large doses after meals and at bedtime (kaolin 15–30 Gm, bis*muth subnitrate 3 75–7 5 Gm) These are* best given in about 60 cc of water Iron is necessary in most cases because of the anemia It often aggravates the diarrhea as well as upsets the stomach, its customary constipating effect being provokingly absent when one desires it most Although usually prescribed after meals it seems to disturb some people less when it is taken immediately before the meal Ferrous sulfate in increasing doses up to 0 6–1 Gm a day is recommended and no advantage in one form of administration over another (tablet, capsule, or liquid) is apparent unless it be to please the patient

Hog s stomach and other intestinal extracts have been used with uncertain results They might be tried for a disease whose treatment by other means is unavailing Twenty four tablets of hog duodenum powder ('viodenum,' 0 5 Gm) are given daily for an indefinite time (months or years) for those who wish and can afford them

While lysozyme concentration is in

malnourished because of unwarranted restrictions that cause great apprehension every time they contemplate a meal.* They should not eat coarse, irritating foods such as raw fruits, uncooked vegetables, berries, melons, celery, cabbage, nuts, and raisins. Equally harmful may be ice cold food and drinks. Weak tea or coffee may be allowed. Tobacco impairs the appetite, the preservation of which is a major problem, and may act unfavorably in other ways. With those who tolerate it well, however, its moderate use may not be harmful. Milk is a palatable, highly nutritious food for most people, but for some reason many patients with ulcerative colitis do not take it well. Whether the intolerance for it is of an allergic nature or is due to the residue it produces is not always certain, but in any case it should be used with caution. It should be sipped slowly, warmed, and always taken with a few plain crackers. Skimmed milk and one of the protein hydrolysates may be given to keep up the protein needs. Positive nitrogen balance can be maintained by diets moderately high in protein with or without the parenteral administration of protein hydrolysate or blood.

An editorial from the *Journal of the American Medical Association* (May 17, 1947) states:

"In general all doctors try to find ways and means of securing for their patients any necessary treatment regardless of cost. However, especially in nutrition, there are times when less costly materials are as good as or better than costly ones. For instance, if plasma is used intravenously purely to furnish protein, it costs at least $1.00 per gram of protein. Suitable digests for intravenous use furnish protein equivalent at less than 10¢ per gram and are often safer to give to the depleted patient because they do not contain the large amount of sodium that plasma does. When it comes to oral feeding, hamburger steak at 40¢ a pound [this was five years ago] furnishes protein at 1 mill per gram, and with it one gets a large quantity of sugar and certain vitamins free. When a patient is seriously depleted of protein and has a deficit of many kilograms, plasma is useless for intravenous feeding and skim milk and skim milk powder are better than steak for oral feedings! This is true not only because of the price but also because so much more can be taken by the patient in a given time."

A program offered by Machella and Miller (*Gastroenterology 10*:28, 1948) may be worthy of trial. It consists of feedings of equal parts of casein and dextrimaltose dissolved in enough boiling water to make a 15 per cent to 25 per cent solution. The mixture should be kept in an ice box and 2 to 4 ounces given every two hours (6:00 A.M. to 10:00 P.M.) for one to two weeks. The efficacy of this mixture is due to its high-calory, readily assimilable, high protein, and low residue content.

When patients are acutely and severely ill it may be necessary to give nothing but warm liquid nourishment by mouth and tide them over with intravenous injections of amino acids, glucose, and saline solutions, and plasma or blood transfusions.

The final diet is of low residue content. It contains lean meat and fish, cooked cereals, rice, macaroni, white or whole wheat bread, potatoes, pureed vegetables, eggs, cottage cheese, and small amounts of cream and butter. Tomato and other vegetable juices may be included. Orange juice is usually desired by most patients and will be more acceptable if diluted in a little hot water. Cold undiluted orange juice, especially on an empty stomach, may upset some people who will therefore decline a nutritious food which they need because of its vitamin C content. While raw fruit must not be taken as long as diarrhea exists, many patients will digest canned and stewed fruits without any ill effect. For des

* See also Chapter 51.

18. Kidney Diseases

I. I RITTER

Acute Glomerulonephritis

ACUTE diffuse glomerulonephritis (acute hemorrhagic nephritis) is a bilateral renal disease characterized by an abrupt onset of edema proteinuria hematuria renal functional impairment and hypertension It is for the most part a disease of youth approximately 70 per cent of the cases occur before the age of 21 The true incidence of the disease is not known since the majority of cases are probably never recognized Under the circumstances the incidence of hospital admissions (0 5 per cent of medical hospital admissions in the United States) gives a false notion of its prevalence

ETIOLOGY

The evidence indicates that acute glomerulonephritis is a sequel of infection with β hemolytic Group A streptococcal organisms in the vast majority of cases Usually the upper respiratory tract is the site of this infection but it may originate in pyogenic infections of the skin the lungs or in infected lymph nodes Scarlet fever and erysipelas are frequently complicated by this disease Other pyogenic organisms such as *Diplococcus pneumoniae Streptococcus viridans* (in subacute bacterial endocarditis) and *Streptococcus anhemolyticus* may be responsible in a few cases of glomerulonephritis

The infection is more apt to be deep seated than superficial Throat cultures taken when the symptoms of nephritis are present are positive for hemolytic streptococci in 70–80 per cent of the cases Antistreptolysin titers a much more sensitive test for previous infection with the streptococcus are significantly elevated in 90 per cent of the cases The degree of elevation of this titer is correlated with the severity of the streptococcus infection and not with the severity of the nephritis

The disease usually makes its appearance following an asymptomatic period after a prior infection ranging from a few days to four weeks the average interval being twelve days In this respect acute nephritis presents a parallel to rheumatic fever where organic involvement follows acute infection by a week or more The mechanisms by which these bacteria bring about an acute glomerulonephritis is not definitely established The bulk of the evidence suggests that they produce renal damage *not* through their direct action on the glomerular capillaries but indirectly through the mediation of altered tissue reactivity or some form of antigen antibody reaction

creased during the highly active phases of chronic idiopathic ulcerative colitis it does not follow that such an excess is an etiological factor in the disease nor that drugs possessing antilysozyme influence will benefit the disease

The use of ACTH and cortisone is still highly experimental During crises of the disease they may be used for a short duration but they are not recommended in any sense whatsoever as a substitute for the more conventional methods of treating the disease

The severely ill patient with ulcerative colitis should be hospitalized In addition to the many details in treatment, repeated transfusions may be required as well as a repetition of laboratory studies for prothrombin time chlorides calcium carbon dioxide combining power and suitable treatment for any emergencies that may arise

SURGERY*

In the absence of complications it is very difficult to decide if and when one should operate for ulcerative colitis The need for operation should be weighed most thoughtfully as the indications for it are hard to define Many patients despite the severity of their attacks have their periods of remission and when these occur one feels very thankful that surgery had not been advised As in peptic ulcer intractability is mentioned as an indication for surgery At once one must ask whether the disease or the patient is intractable? If the former, operation may promise something if the latter nothing Violent acute cases in which one may be most tempted to operate in order to save a life are great surgical risks which as a rule are best avoided Chronic and continuously ill patients who are threatened with invalidism despite good care and cooperation with the physician should be considered for surgery Patients with complications that obviously will not respond to conservative measures or in whom it is not advisable to risk the development of a malignant process will require surgery Complications requiring surgery are polyps or other growths perforation of the bowel, fistulas and abscess formations strictures of the bowel and recurrent massive hemorrhages

The best surgical procedure is ileostomy followed at a later date (about six months) by colectomy * Before an ileostomy is performed careful search should be made for regional ileitis which is not rarely associated with ulcerative colitis Vagotomy and other neurosurgical approaches for controlling idiopathic ulcerative colitis are experimental in nature and are not recommended for its management at this time

When one considers the gratifying results reported by some surgeons of large experience in this disease possibly more thought should be given to earlier operative intervention Whatever dread of a permanent ileostomy has been felt in the past by the patient or by the physician has been largely dispelled by the Koenig Rutzen ileostomy bag which overcomes to a great extent the objectionable features resulting from the operation Recent improvements in this bag have been made The mortality from properly performed operation is so low that it is practically negligible In any event constant close cooperation between the physician and surgeon shows greater benefit for the patient than in most disease conditions

*See also Chapter 42

convulsions Visual disturbances may precede or follow the convulsion The episodes of encephalopathy last for a day or two and spontaneously regress with a fall in the blood pressure or as a result of appropriate treatment

Cardiac failure is most often associated with elevated blood pressure especially a rapidly rising pressure, but it may occur in the absence of hypertension Electrocardiographic abnormalities have been demonstrated in 60–90 per cent of patients at some time during the course of acute glomerulonephritis and consist of inversion of the T wave and depression of the ST segment with reciprocal changes in the third lead

Heart failure accounts for about one third of the deaths in this disease Left ventricular failure may occur suddenly with the appearance of acute pulmonary edema and requires immediate treatment if the patient is to survive * The more usual picture of congestive failure with cardiac enlargement, tachycardia, gallop rhythm, swollen neck veins and enlarged tender liver is usually present in those patients whose treatment has been neglected

Uremia in acute glomerulonephritis is relatively rare and usually follows anuria or prolonged oliguria Hypertensive encephalopathy and cardiac failure may aggravate the nephritis sufficiently to bring about a uremia Once uremia has developed the prognosis is very poor

PROGNOSIS

The prognosis depends upon the patient's age, the degree of renal involvement, the presence or absence of cardiac failure and its response to treatment and how early the disease is recognized In children complete recovery occurs in about 90 per cent of the cases but in adults this figure is reduced to 50–60 per cent The presence of anuria at the onset of the disease usually implies extensive involvement of the glomeruli and makes the prognosis grave Cardiac failure is a very serious complication of acute glomerulonephritis and is responsible for many deaths That early recognition of the disease and the institution of proper therapy will prevent acute cardiac failure and other complications has been recognized by clinicians for many years Chronic glomerulonephritis seldom develops in those patients who receive medical care early during the initial attack of nephritis

TREATMENT

The prevention of acute glomerulonephritis depends upon the proper recognition and adequate treatment of streptococcal diseases Once such a disease is suspected, penicillin should be given in doses of 300 000 units intramuscularly every twelve hours Repeated dosage of penicillin during the first few days of the infection is more important than the size of the individual dose The penicillin will suppress the antigen and the subsequent formation of auto-antibodies such as antistreptolysin

Bed Rest Once the disease has developed it becomes essential to keep the patient at bed rest until the major clinical symptoms and signs have disappeared Not only does clinical experience demand such rest but there is ample experimental evidence to underline the need for this measure Studies were conducted by Bradley on patients with acute glomerulonephritis before and during the assumption of the upright position He found that the glomerular filtration and renal blood flow diminished and the blood pressure rose when the patients assumed the upright position Furthermore, the flow of urine fell sharply and there was a striking reduction in the output of sodium and potassium in the urine The urine became grossly bloody and proteinuria increased These changes predispose to edema formation and

* *See* Chapter 10

CLINICAL COURSE

The clinical picture of acute glomerulonephritis varies greatly On the one hand there may be nothing more than a proteinuria detected in the routine examination of the urine on the other hand the complete syndrome of heart failure hypertensive encephalopathy and uremia may appear

In the usual case the disorder may begin abruptly with the appearance of edema which has a tendency to localize about the eyes and cheeks although all parts of the body may be involved At the same time the urine may become smoky or coffee colored and the urinary output may diminish strikingly There may be some burning on urination and dull aching over the lumbar region Headache especially on awakening may be present and the patient may complain of anorexia nausea or vomiting and abdominal distention The initial symptoms especially in children, may be convulsions and projectile vomiting or the clinical picture may be dominated by symptoms of heart failure such as dyspnea oppression in the chest palpitation and cough

Physical examination will reveal a waxy pallor edema of the eyelids and cheeks and evidence of recent inflammation of the throat and tonsils The blood pressure may be normal but is moderately elevated in about 60–70 per cent of the cases The pulse rate may be slow but where heart failure is present the rate is quite rapid The size of the heart is normal in the majority of cases but in about 20 per cent of the patients it is enlarged because of frank heart failure The heart tones will vary according to the state of the heart gallop rhythm may be present. Other signs of heart failure such as orthopnea basilar râles and an enlarged tender liver may be found

Urine

The output of urine per twenty four hours is reduced to 400–500 cc but may be diminished to the point of anuria in the severest cases The specific gravity is rather high in the first few days but has a tendency to fall as the distal tubular function becomes more impaired The presence of a persistently high specific gravity during oliguria in acute nephritis should raise the suspicion of prerenal deviation of water such as might occur in heart failure or vomiting

The urine practically always contains blood protein and casts and appears to be smoky or coffee colored Gross hematuria is present in about 50 per cent of the cases Early in the course of the disease there are hyaline and epithelial casts but later epithelial granular and red blood cell casts make their appearance Polymorphonuclear leukocytes and epithelial cells are also present in large numbers In other cases the hematuria is microscopic but there is no correlation between the degree of hematuria and the severity or progress of the disease Proteinuria is usually quite marked but there are occasionally patients in whom proteinuria is only slight The protracted excretion of large quantities of protein should make one suspect the presence of a nephrotic syndrome

The blood nonprotein nitrogen is usually elevated depending upon the degree of glomerular involvement and other factors The concentrating power of the kidney is reduced early and is the last to return to normal during recovery The phenolsulfonphthalein test is a sensitive measure of renal function and is impaired early in the course of the disease

Complications

The three most serious complications of acute glomerulonephritis are hypertensive encephalopathy cardiac failure and uremia

Hypertensive encephalopathy may appear following a sudden rise in the blood pressure Severe generalized headaches drowsiness and vomiting are followed by

intramuscularly in appropriate dosage and with proper precautions The newer hypotensive drugs such as hexamethonium chloride ('methium') and 1 hydrazinophthalazine hydrochloride (apresoline) are still in the experimental stage and should not be employed for the present Hexamethonium in particular may be dangerous in acute glomerulonephritis since in clinical experience deaths from acute renal failure have resulted following sudden and prolonged drop in the blood pressure

Lumbar puncture has been employed for relief of hypertensive encephalopathy It *usually does not give convincingly beneficial* results

The treatment of cardiac failure is not essentially different from the treatment of this condition from any other cause *

Anuria. The treatment of anuria presents the physician with a difficult problem If evidence of prerenal dehydration *is present as a result of prolonged anorexia* nausea, diarrhea, or vomiting, and if edema and pulmonary congestion are absent it is permissible to administer up to 3 liters of fluid including one liter of isotonic solution of sodium chloride during one twenty four hour period If the patient responds with a diuresis the treatment is continued if there is no increase in urinary output no great harm has been done and the treatment is discontinued If the anuria persists for more than a few days, it will be necessary to resort to the artificial kidney (where this is available) or to the intermittent *peritoneal lavage as described by Grollman* * In the meantime the patient should be maintained on carbohydrate and fat without protein or electrolytes and with rigid restriction of fluids † Diuretic drugs are definitely contraindicated in acute glomerulonephritis

*See Chapter 10

* See p 396
† See p 395

The Nephrotic Syndrome

THE nephrotic syndrome is characterized by heavy proteinuria, marked hypoproteinemia, intractable edema, and hyperlipemia The appearance of these phenomena in the absence of heart failure is quite striking and is easily recognized It is encountered most frequently in chronic glomerulonephritis but may also be found in intercapillary glomerulosclerosis (Kimmelstiel Wilson syndrome) amyloidosis, syphilis, poisoning with certain chemical agents notably carbon tetrachloride and in renal vein thrombosis

In its most characteristic form it is seen in children and young adults as the so called true or lipoid nephrosis Most internists are of the opinion that this condition is a form of unrecognized glomerulonephritis Others, however, and especially the pediatricians, feel that this disease is unique and results either from intrarenal disturbance of protein metabolism or from a specific renal lesion Whatever the etiology or pathogenesis of the syndrome, the therapeutic approach is in many respects the same

TREATMENT

Edema

To the patient his edema is the most disabling manifestation In fact so striking is this sign that even the physician is apt to forget the profound metabolic disturbances which are masked by the edema

As is true of the treatment of all general edema rigid restriction of salt is necessary

nitrogen retention as well as to urinary abnormalities

The exact length of time for maintaining bed rest has been the subject of dispute but the consensus is that it should be maintained until the major signs and symptoms of the disease have disappeared Since a mild proteinuria and microscopic hematuria *may persist* for as long as one year it is obviously impractical to keep some patients in bed until these abnormal findings have disappeared Return to activity should be gradual and repeated examinations of the urine should be used to guide the physician in the treatment of these patients

Diet The diet is essential in the treatment of some of the major manifestations of this disease Rigid restriction of sodium in any form is important The daily fluid intake should be limited to the volume of urine excreted in twenty four hours plus an allowance of 500–1000 cc for the loss of fluid from the lungs and skin These measures will prevent edema and reduce the incidence of cardiac failure and hypertension when oliguria or anuria are present

The diet should be the same as employed in lower nephron nephrosis In order to reduce *protein* catabolism to a minimum the diet should be limited to fat and carbohydrates with enough calories to prevent endogenous protein breakdown Fat emulsions and sugar should be used as the mainstays of the diet Fruit juices are to be avoided since they are rich in potassium The high fat high-carbohydrate diet will prevent a rapid rise in the nonprotein nitrogen of the blood and the acidosis produced by the accumulation of phosphates and sulfates will be prevented

In case of anorexia or vomiting food and fluid must be given *intravenously* For this purpose a twenty per cent solution of invert sugar may be employed It should contain adequate quantities of vitamins B and C Electrolytes should be rigidly excluded since they may cause serious disturbances In case of severe deficit of certain electrolytes caused by vomiting or diarrhea they may be replaced cautiously and only after careful analysis of the blood chemistry

In mild cases with good renal function a diet containing 25–30 Gm of protein and 50 calories per Kg body weight is permissible Infants and younger children require a higher caloric intake and may be permitted up to 1 5 Gm of protein per Kg body weight If proteinuria is mild and hypertension is absent, rigid restriction of salt is not necessary and the patient may be permitted 1–2 Gm of salt per day

Hypertensive Encephalopathy The treatment of hypertensive encephalopathy is of the greatest importance Sedation with barbiturates or by magnesium sulfate given parenterally is valuable in reducing the blood pressure and in preventing headaches The magnesium sulfate may be given intramuscularly as the 50 per cent solution (0 1–0 2 cc per Kg body weight per day) in divided doses If the blood pressure comes down to a satisfactory level on this therapy it can be maintained by the administration of 15–30 cc of the 50 per cent solution orally two to three times a day Where the oral or intramuscular use of magnesium sulfate is ineffective it is necessary to resort to the intravenous injection of 100–200 cc of a 1 per cent solution The injection must be given slowly and the patient's blood pressure and respirations must be observed carefully A solution of 10 per cent calcium gluconate must be immediately injected intravenously if respiratory depression occurs Therapy with magnesium sulfate is quite effective in reducing the blood pressure and in controlling the manifestations of hypertensive encephalopathy

More recently vasodilators of the veratrum viride group ("Veriloid and others) *have been employed successfully* for this purpose These are given intravenously or

main disease This method must be used with great caution

Hormones A number of hormones have been used to control nephrotic edema Thyroid, once widely used has been abandoned and posterior pituitary extracts have been found to be valueless More recently corticotropin (ACTH) and cortisone have been used in attempts not only to alleviate edema but also in the hopes of effecting a cure The latter hope has unfortunately not been realized The dosage of ACTH varies from 50 to 100 mg daily for from five to ten days More than one course may be necessary to initiate diuresis During the initial days of treatment there is further retention of sodium and water After treatment is discontinued there is a withdrawal diuresis and more or less reduction in proteinuria with an increase in the levels of the plasma protein and albumin and a reduction in the serum cholesterol When reduction in proteinuria occurs an improvement in the urinary sediment is usually observed About 60 per cent of the patients treated respond with a diuresis Cortisone acts similarly to ACTH but on the basis of reports is not as effective Perhaps the difference is explained by the fact that 100 mg of ACTH stimulates the production of more cortisone than the 100 mg of cortisone usually employed

The duration of remission following treatment with ACTH or cortisone varies greatly It may be interrupted by an intercurrent infection or there may be a gradual recurrence of proteinuria without obvious cause However it is possible to get sustained improvement which lasts for many months At best then these hormones offer only a means of controlling the nephrotic edema

Paracentesis When all measures designed to alleviate the edema fail and the patient accumulates fluid in the pleural and peritoneal cavities it may be necessary to try the mercurial diuretics or to remove these fluids by mechanical means Paracentesis should be done only if there is respiratory or cardiac embarrassment This is a palliative measure in the majority of patients as the fluid will reaccumulate shortly Whenever paracentesis is performed penicillin in full doses should be given for a period of thirty six hours

Maintenance of Nutrition

Extensive wasting of all the tissues in the body is characteristic of the nephrotic syndrome In an effort to maintain a positive nitrogen balance and to promote the synthesis of plasma proteins most clinicians have employed a high protein diet It has been shown however, that increased synthesis does not result from an increased protein intake and that a diet containing more than 3 Gm of protein per kg body weight may actually be detrimental To build up lost tissue protein the diet should contain a normal amount of protein plus the amount lost in the urine The carbohydrate and fat content should be higher than normal for the given age and ideal weight of the patient Calcium and vitamin D supplements should be supplied in the diet

General Symptomatic Treatment

Bed rest is important whenever edema is massive or where there is evidence of active glomerulonephritis Renal blood flow may be diminished by fatigue and the upright position favors the reabsorption of salt and water from the renal tubules Small transfusions should be given if anemia is present and dehydration must be carefully guarded against and promptly corrected since it may lead to a reduction in the circulating blood volume and a proportionately greater reduction in renal blood flow Marked disturbance in the electrolyte pattern and acid base balance of the blood secondary to diarrhea vomiting etc must be corrected regardless of ensuing edema

Salt free bread must be used as well as sodium free milk solids When the patient is able to excrete 1 5–2 Gm per day as sodium chloride a diuresis may follow sharp restriction of sodium intake When however, the patient excretes only minimal quantities of sodium no diuresis follows the restriction of sodium in the diet Although such a diet is not very effective in reducing edema it is well known that a high sodium intake markedly aggravates nephrotic edema and should, therefore, be avoided

Since sodium restriction is frequently without effect other methods or combinations of methods have been employed in the treatment of edema It has been believed for years that the diminished oncotic pressure of the blood due to low plasma protein was one of the major factors in the production of such edema It was reasoned therefore that if substances which were capable of raising the oncotic pressure were added to the blood the edema would be reduced One of the earliest materials employed for this purpose was gum acacia This gave favorable results in a number of instances but lost favor because of its toxic effects on the liver and possibly on the kidneys Whole blood serum and plasma transfusions have been tried repeatedly with disappointing results Solutions of gelatin have been used but were found to be too toxic Solutions of dextran have been used experimentally with promising results but more work will be required to determine their usefulness in the treatment of nephrotic edema

Salt Poor Human Albumin The use of salt poor human albumin has met with success in about 50 per cent of the cases treated This is an expensive form of treatment and has the further disadvantage of being of only temporary value Nevertheless it is indicated in children who are severely edematous are unresponsive to other forms of therapy, and are unable to eat because of ascites

In children the starting dose is 25 Gm per day, which may be increased to 30–40 Gm per day as necessary Usually one to two weeks of daily injections are necessary to produce diuresis It can be given diluted in glucose solution or as a simple twenty five per cent solution The former should be employed in patients with elevated blood pressure It must be given slowly (1–2 cc per minute) to avoid harmful effects

Diuretics Diuretics have been uniformly disappointing in the treatment of nephrotic edema The xanthine derivatives are of no value in augmenting the excretion of sodium The organic mercurial diuretics although shown to have a wide margin of safety in the treatment of cardiac edema are not without danger in nephrosis and since their effectiveness is limited ordinarily should not be employed Ammonium chloride may be dangerous particularly when kidney function is impaired since it may lead to severe acidosis and further impairment of renal function

The diuretic of choice in the nephrotic patient is urea It is harmless when given in fairly large doses (40–60 Gm per day in divided doses) and for long periods of time Tart fruit juices should be employed as a vehicle If it is effective as a diuretic the results will be apparent in three days If no effects are seen at the end of one week it should be discontinued

Striking remissions have occurred in nephrosis after attacks of measles and other virus infections with cutaneous manifestations Janeway deliberately inoculated nephrotic children with measles virus Penicillin was given in full doses to prevent any secondary manifestations Diuresis was produced in many cases but the length of remission was variable and there was little or no permanent effect on the course of the

maximum tubular transfer mechanisms indicate a marked disturbance of tubular function due both to loss of tubules and to abnormal function of the remainder. Further evidence of disturbed tubular function consists of (1) loss or impairment of synthesis of ammonia, (2) defective reabsorption of base with the loss of large quantities of sodium and other cations in the urine, (3) diminished reabsorption of water and loss of concentrating power. The loss of the power to concentrate by the distal tubules causes the urine to become dilute, increases its volume, and changes the pattern of the daily output. Damage to the tubule in the late stages of this disease may exceed glomerular damage so that more filtrate is formed than the damaged tubule can handle. Studies of the renal blood flow indicate a reduction in the absolute quantity circulating through the kidney, but when this flow is compared with the reduced number of nephrons there is evidence that there is increased blood flow to the functioning parenchymal tissue.

The course is highly erratic. Damage to the glomerulus and/or tubule and glomerulo tubular imbalance may cause the loss of electrolytes and water, the retention of anions and various metabolites, or the loss or retention of cations such as potassium. These lead to a great variety of symptoms.

SYMPTOMS AND COURSE

The patient with latent glomerulonephritis is usually completely free of symptoms. The only abnormal finding is the presence of proteinuria, which may be slight and is frequently discovered accidentally in the course of a routine physical examination. Repeated examinations of the urine will show not only persistent proteinuria but also occasional microscopic hematuria. Such patients may continue to be free of symptoms for many years but sooner or later they will develop the typical picture of chronic glomerulonephritis and more and more of the renal parenchyma is destroyed.

In another group of patients the clinical picture is dominated by hypertension. Edema is usually absent and the urine may show only slight proteinuria and cylindruria. The clinical course is parallel to that of hypertension and the progress of the renal lesion is slow. Sooner or later these patients develop the cardiac and cerebral complications of hypertension and with their appearance the reduction in renal function is accelerated and uremia ensues.

Patients who develop the nephrotic stage have been described elsewhere in this chapter.

Exacerbations often occur in the course of chronic glomerulonephritis. These are usually brought about by infection with the hemolytic streptococcus and less frequently by other factors such as trauma and major surgery. In contrast to the long latent period before the appearance of symptoms in acute glomerulonephritis, the symptoms of the exacerbation appear in twenty-four to forty-eight hours following the infection and are manifested by an increased proteinuria and hematuria. Edema, rise in blood pressure, malaise, and other symptoms may or may not appear. How much additional damage the exacerbation has caused will become evident only after careful examination of the urine and careful evaluation of renal function studies.

TREATMENT

Chronic pyelonephritis should be prevented, if possible, by adequate treatment of the acute glomerulonephritis. This has been described previously. The treatment of an acute exacerbation does not differ materially from the treatment of the initial attack.

If the patient's renal function is fairly good he should be permitted to regulate his own life but should be cautioned about exposure to cold and indulgence in strenuous

However it is enough to bring the electrolytes to a level consistent with the patient's comfort rather than to bring it up to normal. During gastrointestinal upsets parenteral feeding may be necessary for a short time.

Infectious diseases, especially upper respiratory infections, should be treated with penicillin or other antibiotics to prevent exacerbation of the renal disease. The sulfonamides may cause renal complications and whenever possible should be avoided. When bacteremia develops, especially in nephrotic children with peritonitis, full doses of antibiotics are indicated at the earliest possible opportunity and vigorous treatment should be continued until the infection has disappeared.

Nephrotic Crisis

Many young children will develop a nephrotic crisis during the course of an intercurrent disease. This consists of a sudden rise in temperature up to 104 degrees or more, severe generalized abdominal pain, nausea, vomiting and prostration. The condition is accompanied by a high incidence of bacteremia and peritonitis. The diagnosis is established by the presence of an amino-acid–nitrogen level below 2.5 mg per 100 cc by the ninhydrin technic. (Farr)

When nephrotic crisis is suspected the child is given 200 000 to 300 000 units of penicillin every four hours. Sulfadiazine is given in doses sufficient to maintain a blood level of 8–10 mg per 100 cc, starting with an initial dose of 0.1 Gm per kg ideal body weight. Simultaneously a rapid intravenous infusion of a 10 per cent protein hydrolysate is given. The total dose administered is calculated on the basis of 0.5–0.75 Gm per kg ideal body weight for a total of 2–2.5 Gm per kg daily. These infusions are given three to four times a day. The chemotherapy and hydrolysate are continued until the temperature returns to normal.

Chronic Glomerulonephritis

IN the majority of patients with acute glomerulonephritis, and this is especially true of children, there is complete recovery and immunity to further attacks of the disease. In a small number death occurs during the acute stage. In a somewhat larger number of patients proteinuria, microscopic hematuria and impaired concentrating power persist, revealing the presence of a subacute or chronic process.

ETIOLOGY AND PATHOGENESIS

Chronic glomerulonephritis has the same etiology as acute glomerulonephritis. It results from the continued destruction of the various elements of the nephron and its blood vessels and is characterized in its terminal stage by complete disorganization of the renal architecture. The kidneys are reduced to less than half their normal weight in the majority of patients with advanced chronic glomerulonephritis. The number of nephrons is much reduced and those that remain are markedly deformed. The destroyed nephrons are replaced by fibrous tissue and this leads to shrinkage of the organ. The blood vessels become rigid and abnormal in their distribution.

It is not surprising therefore that an extreme variety of functional derangements should exist. Measurements made by Bradley indicate greatly depressed glomerular filtration rates caused by the widespread obliteration of glomeruli and studies of

maximum tubular transfer mechanisms indicate a marked disturbance of tubular function due both to loss of tubules and to abnormal function of the remainder Further evidence of disturbed tubular function consists of (1) loss or impairment of synthesis of ammonia (2) defective reabsorption of base with the loss of large quantities of sodium and other cations in the urine (3) diminished reabsorption of water and loss of concentrating power The loss of the power to concentrate by the distal tubules causes the urine to become dilute increases its volume and changes the pattern of the daily output Damage to the tubule in the late stages of this disease may exceed glomerular damage so that more filtrate is formed than the damaged tubule can handle Studies of the renal blood flow indicate a reduction in the absolute quantity circulating through the kidney but when this flow is compared with the reduced number of nephrons there is evidence that there is increased blood flow to the functioning parenchymal tissue

The course is highly erratic Damage to the glomerulus and/or tubule and glomerulo tubular imbalance may cause the loss of electrolytes and water, the retention of anions and various metabolites or the loss or retention of cations such as potassium These lead to a great variety of symptoms

SYMPTOMS AND COURSE

The patient with latent glomerulonephritis is usually completely free of symptoms The only abnormal finding is the presence of proteinuria which may be slight and is frequently discovered accidentally in the course of a routine physical examination Repeated examinations of the urine will show not only persistent proteinuria but also occasional microscopic hematuria Such patients may continue to be free of symptoms for many years but sooner or later they will develop the typical picture of chronic glomerulonephritis and more and more of the renal parenchyma is destroyed

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activities The diet need not be too restricted and enough protein should be provided to maintain nitrogen balance, prevent anemia and offer the patient a palatable diet It should provide 1 gm of protein per kg body weight per day for the adult (and a proportionately higher figure for growing children) If glomerular filtration falls to preuremic levels the protein intake should be cut down to 0 5 gm per kg body weight per day

In the absence of edema the salt intake should be normal but if edema is present in chronic nephritis the salt should be restricted but not too rigidly since it is more important to maintain the patient s appetite and nutrition than to control the edema The treatment of the nephrotic syndrome has been described previously

Cardiac Failure

The treatment of cardiac failure is quite important Left ventricular failure should be recognized early and should be treated by rest digitalization salt restriction sedation and whatever additional measures may be necessary The management of the hypertension is essentially the same as in essential hypertension* except that sympathectomy is not effective since nephritic hypertension is of humoral origin In addition, rigid restriction of salt may be quite dangerous in these patients, especially those who have a tendency to lose salt

Anemia in this disease is common and may be due to severe and protracted dietary restriction in latent glomerulonephritis, or to severe protein depletion in the nephrotic syndrome or to the suppression of bone marrow function in the later stages of severe renal impairment If dietary restriction is the cause, the anemia may be corrected by diet adequate in proteins and by the administration of iron Whole blood transfusions must be employed in treating the anemia of the nephrotic syndrome In the anemia of renal insufficiency, iron liver folic acid and vitamin B_{12} preparations are of no value Repeated transfusions of whole blood or packed red cells are the only effective means of combating this anemia The physician must have complete confidence in the typing and cross matching of the blood since a transfusion reaction will have disastrous effects on the already damaged kidneys

* See also Chapter 15

Pyelonephritis

THE most important group of renal diseases from the point of view of incidence and of susceptibility to therapy is the pyelonephritides These are infections of the kidney due to common bacteria and are therefore susceptible to treatment with our modern drugs The acute stage is the most common disease of the kidney and in childhood probably ranks second in frequency only to the upper respiratory infections The chronic stage is more often seen than chronic glomerulonephritis and is responsible for a high percentage of examples of necrotizing arteriolitis (malignant hypertension)

The disease is present in all age groups from infancy to old age In the former it is frequently associated with congenital abnormalities and in the latter with obstruction secondary to enlargement of the prostate and to carcinoma of the uterus It is encountered frequently in pregnancy and in the diabetic. Because of its protean manifestations and insidious course the

acute stage is frequently permitted to go into the chronic stage since there is no continuity of observation Thus many patients who might otherwise have been cured are ultimately seen in the uremic or suburemic stage when much destruction of renal tissue has taken place and when treatment offers few rewards either to the patient or to the doctor

ETIOLOGY AND PATHOGENESIS

The bacteria responsible for the infection for the most part belong to the coli aerogenes group It has been estimated that the offending organism responsible for acute pyelonephritis in children is *Escherichia coli* in as high as 80 per cent of the cases Other organisms found are *Aerobacter aerogenes Proteus vulgaris Pseudomonas aeruginosa Streptococcus fecalis, Streptococcus pyogenes* and *staphylococcus aureus* In the acute stages the offending organism is usually a single one Mixed infections are common in the chronic cases

Most often the organisms reach the kidney by way of the *circulation* Less frequently they invade the kidney along the lymphatics or by reflux of the infected bladder urine In acute pyelonephritis the invasion of these micro-organisms produces multiple inflammatory foci scattered throughout the interstitial tissue They are found adjacent to blood vessels and may consist of a few organisms surrounded by a *collection of polymorphonuclear leukocytes* and monocytes or there may be frank abscess formation The tubules may contain pus and bacteria only if the nephron has been invaded The pelvis is acutely inflamed If the infection clears up (as it does in the vast majority of cases) the inflammatory foci are replaced by scar tissue but enough normally functioning renal tissue remains to make the scarred kidney undetectable clinically

Repeated acute attacks or continuous smoldering infection in time *leads to a shrinking of the kidney and destruction of* many nephrons The interstitial tissue contains increased amounts of fibrosis and infiltrations of lymphocytes and plasma cells The tubules in the involved area are dilated lined with flattened epithelium and filled with colloid like material which has a remarkable resemblance to thyroid tissue Periglomerular fibrosis is present and medial hypertrophy of the small vessels is found The pelvis is infiltrated with lymphocytes and plasma cells Normal tissue is found between the affected areas With continuing infection more and more destruction of nephrons takes place with replacement of formerly functioning tissue by scar tissue In time too little of the former remains to support life

It can be seen from the above that this is not a disease of the nonfunctioning conduits which the name pyelitis implies but is one that involves the nephrons blood vessels and lymphatics of the kidney Hence the term pyelitis with its implication of a benign suppurative disease of the pelvis should be dropped from medical terminology

CLINICAL COURSE

Acute Pyelonephritis

In acute pyelonephritis the symptoms vary considerably depending upon the age the severity of the infection and the type of organism In children and young adults *the onset is usually abrupt with* high fever chills flank pains and occasionally abdominal pains accompanied by nausea and vomiting Usually there is painful micturition frequency, and urgency as well as tenderness and muscle spasm over the costovertebral angle On rare occasions there may be no symptoms pointing to the urinary tract at first

In older patients the fever may be lower and the pains over the flank may be less marked In such infections spiking temperatures and drenching sweats are com

activities The diet need not be too restricted and enough protein should be provided to maintain nitrogen balance, prevent anemia, and offer the patient a palatable diet It should provide 1 gm of protein per kg body weight per day for the adult (and a proportionately higher figure for growing children) If glomerular filtration falls to preuremic levels the protein intake should be cut down to 0 5 gm per kg body weight per day

In the absence of edema, the salt intake should be normal but if edema is present in chronic nephritis the salt should be restricted but not too rigidly since it is more important to maintain the patient s appetite and nutrition than to control the edema The treatment of the nephrotic syndrome has been described previously

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THE most important group of renal diseases from the point of view of incidence and of susceptibility to therapy is the pyelonephritides These are infections of the kidney due to common bacteria and are therefore susceptible to treatment with our modern drugs The acute stage is the most common disease of the kidney and in childhood probably ranks second in frequency only to the upper respiratory infections The chronic stage is more often seen than chronic glomerulonephritis and is responsible for a high percentage of examples of necrotizing arteriolitis (malignant hypertension)

The disease is present in all age groups from infancy to old age In the former it is frequently associated with congenital abnormalities and in the latter with obstruction secondary to enlargement of the prostate and to carcinoma of the uterus It is encountered frequently in pregnancy and in the diabetic Because of its protean manifestations and insidious course the

full dosage If the response to treatment is unsatisfactory the sensitivity of the organism to various other drugs should be determined Treatment should be continued until pyuria has disappeared and at least three repeated cultures of the urine at intervals of several days show no further growth

If the urogram indicates any source of obstruction to the flow of urine, the abnormality causing the obstruction must be corrected by a urologist as soon as the acute infection is brought under control

Symptomatic treatment consists of adequate hydration This is particularly important in children Where there has been loss of fluids and electrolytes through vomiting or diarrhea it is necessary to replace these by parenteral means if necessary Analgesics and sedatives are used as indicated and good nursing is essential during the bouts of fever chills and sweats

Chronic Pyelonephritis

Prevention represents the best treatment for chronic pyelonephritis This is most effectively accomplished by eradication of infection in every case of acute pyelonephritis and by early recognition and relief of obstruction in the urinary tract As long as a large prostate calculi and other obstructive lesions are present infection cannot be eradicated Failure to recognize this will lead to chronic infection and gradual destruction of the kidney parenchyma Chemotherapy is very important and should be guided by repeated cultures of the urine and bacterial sensitivity studies In contrast to acute pyelonephritis the cultures of the urine in chronic pyelonephritis will show the presence of more than one organism which may require the use of combined therapy with several chemotherapeutic agents

Certain of the gram negative bacilli of the *Aerobacter, Proteus* and *Pseudomonas* type frequently present in chronic pyelonephritis may be extremely resistant to therapy and repeated courses of treatment with full doses of different drugs may be necessary

Any febrile episode in a patient with chronic pyelonephritis should raise the suspicion of recurrent infection of the kidney Bed rest, examination of the urinary sediment, culture of the urine and chemotherapy should be instituted

Later in the course of the disease hypertension, hypertensive heart failure and renal insufficiency appear These are treated according to the methods discussed elsewhere *

* See Chapters 15 and 10

Lower Nephron Nephrosis

LOWER nephron nephrosis is a syndrome characterized by oliguria or anuria hematogenous pigment excretion hypertension and uremia Because it is precipitated by many conditions including such widely used modes of therapy as blood transfusions and the sulfonamides every practicing physician is likely to encounter this syndrome Since the disease is self limiting many lives can be saved by the physician who properly understands its course and therapy

ETIOLOGY

Lower nephron nephrosis may occur in a wide variety of conditions including incompatible blood transfusions crush injuries shock from any cause sulfonamide

mon Severe prostration, abdominal distention and other signs of ileus may ensue Bacteremia may be encountered in these cases as well as leukocytosis and severe anemia

The urine is usually concentrated and turbid It contains a moderate quantity of protein and the sediment shows many pus cells many clumps and bacteria on direct smear Microscopic hematuria is not unusual and pus cell casts as well as finely granular casts may be present Renal function is intact and the urogram is usually normal Culture of the urine is important It will not only isolate the causative organism but will be a guide to therapy

Provided there is no obstruction to drainage the course of acute pyelonephritis is usually short The infection subsides without residual damage to the kidney and there may be no recurrence

In a certain number of these patients there will be recurrent episodes of chills fever backaches and dysuria Whether this is caused by a continuously smouldering infection or a complete healing of the initial infection with recurrence the end result is the same—progressive destruction of renal tissue leading to chronic pyelonephritis

Chronic Pyelonephritis

The diagnosis of chronic pyelonephritis may be quite difficult A history of repeated attacks of acute pyelonephritis is of value but there are a number of patients in whom this is lacking and whose first symptoms are those due to chronic uremia The complaints consist of fatigue anorexia, slight nausea gradual loss of weight pallor and dryness of the skin with a peculiar brownish discoloration Characteristically these patients have nocturia and perhaps some frequency of urination Edema (in absence of heart failure) is lacking Despite these symptoms the patients usually are in surprisingly good physical condition, considering their poor renal function

TREATMENT

Before treatment is undertaken it is well to recall that pyelonephritis is a disease involving the interstitial tissue and not the nonfunctioning conduits Hence the concentration of the therapeutic agent in the blood must be high enough to be effective in the tissues Secondly the presence of obstruction or stasis will prevent the complete eradication of infection no matter what therapeutic agent is employed and will lead to continuous or recurrent infection of the kidney with its lethal end results

Hence *every* patient should have a careful history and physical examination a careful examination of the urine (and especially of the sediment) repeated cultures of the urine to isolate the offending organism and to determine its sensitivity to various drugs and finally if possible an excretory urogram These are the minimal steps necessary Additional tests may be used as indicated

Acute Pyelonephritis

In acute pyelonephritis the specific antibiotic treatment will depend upon the results of the culture but treatment should be started at once with a drug having a wide antibacterial spectrum Since the offending organism is most often a gram negative bacillus penicillin is usually of little value The drugs of choice are the sulfonamides especially gantrisin and the wide spectrum antibiotics chloramphenicol aureomycin and terramycin * Streptomycin while theoretically an ideal drug for the treatment of urinary infections has been disappointing because of the extremely rapid development of streptomycin resistance on the part of the organisms

The drug employed should be used in

* See also Chapter 4

illness is relatively brief, in fatal blood transfusions the survival period is usually from three to ten days in the cases reported by Lucke 75 per cent of the deaths occurred within the first eight days Hence, if the patient survives to the tenth day his chances of recovery are excellent The reported mortality statistics vary from 17 5 per cent to 90 per cent It is the present consensus that the latter figure is needlessly high and reflects poor management of the disease

At the end of ten to fourteen days spontaneous diuresis occurs introducing the third stage of this disease The quantity of urine passed in twenty four hours may reach 5000 cc or more with consequent loss of large quantities of salt (up to 20–30 Gm per day) the loss of salt and water may produce severe dehydration and hypochloremia The marked diuresis which lasts for about four to five days is followed by more advanced recovery with conservation of salt and water During this recovery period the blood pressure reverts to normal the proteinuria and formed elements in the urine disappear gradually the azotemia disappears and the electrolyte pattern returns towards normal However the isosthenuria may continue for a month or longer and normal kidney function as measured by clearance studies may not be established for many months

The clinical development of the syndrome is accompanied by certain histologic features which develop in orderly sequence The initial change which occurs eighteen to twenty four hours after injury consists of lipoid degeneration in the epithelium of the ascending loop of Henle This is followed within twenty four to seventy two hours from onset by precipitation of pigment in the distal convoluted and collecting tubules Occasionally on the third day and regularly on the fourth or fifth day necrosis occurs in the ascending loop of Henle and distal convoluted tubules simultaneously with beginning regeneration of the epithelium At the same time lymphocytes appear between the tubules and around the vessels If the patient recovers complete healing of the lesions takes place

TREATMENT

As in all serious diseases prevention is the most important aspect of treatment The utmost care must be exercised in the technics of blood transfusion every effort must be made to prevent shock and dehydration when present they must be treated promptly and adequately Caution must be exercised in the use of the older sulfonamides especially sulfathiazole proper safeguards must be taken when industrial chemicals such as carbon tetrachloride are used *

The physician who treats acute renal insufficiency must understand the underlying process he should realize that the disease is reversible and self limited and that intelligent care can bring complete recovery The chief aim of treatment is to keep the patient alive for seven to fourteen days until spontaneous diuresis sets in

Shock and Dehydration † The first step in treatment is to overcome shock and dehydration Anemia or hypovolemia with hypotension are treated with adequate volumes of whole blood The clinical picture and degree of hemodilution must be used as guides to therapy Needless to say great care must be taken to insure the compatibility of the infused blood When blood is not promptly available and the hypotension is severe solutions of plasma or concentrated albumin should be employed

Oliguria When the patient enters the second or oliguric phase of the disease the physician must refrain from forcing the administration of parenteral fluids in an effort to increase the production of urine The unwise administration of *fluids* has been responsible for the death of many

* See Chapter 50

† See also Chapters 19 and 43

reactions, hemolysis of blood produced by distilled water during transurethral prostatectomy, blackwater fever, heat stroke, uteroplacental hemorrhage, and fulminating infections (particularly of the gastrointestinal tract when rapid loss of fluids and electrolytes play a large role in precipitating the syndrome) It may occur in association with acute yellow atrophy, particularly that produced by chemicals such as carbon tetrachloride and chloroform *

CLINICAL MANIFESTATIONS

Although the clinical symptoms and signs vary somewhat with the etiologic circumstances the course of the disease generally falls into three phases (1) the shock phase (2) the phase of renal insufficiency and (3) the phase of diuresis and recovery

*In the majority of cases shock, which fol*lows shortly after the initial insult, presents the classic and unmistakable signs of lowering of the blood pressure ashen gray pallor cold sweat and tachycardia In the cases in which the signs are not so obvious the existence of shock can be determined by certain tests such as the specific gravity of the blood and hematocrit determinations which by indicating the presence of hemoconcentration reflect a decrease in the circulating blood volume Shock usually responds to appropriate therapy and the patient's condition seems to be satisfactory within twenty four hours †

Recovery from shock is followed by the second phase of the disease which is characterized by oliguria and renal insufficiency During this stage which usually lasts from one to twelve days most of the deaths from uremia occur Oliguria is severe and may progress to anuria The reduction in output of urine that appears during the stage of shock is at first not a matter of concern since shock itself produces anuria or oliguria However, despite continued treatment with fluids the oliguria persists in twenty four hours the patient may pass 500 cc. or less of urine, which is highly acid with the specific gravity fixed around 1 010 The urine, which may be frankly bloody or smoky for one to two days yields a positive result in the benzidine test * thus indicating the presence of some hematogenous pigment The latter disappears by the third or fourth day Proteinuria is present from the onset in practically all cases the sediment contains red blood cells white blood cells granular casts, and pigmented casts that are important in the diagnosis of this disease

Studies of the blood chemistry show a rapid rise in serum urea nitrogen and creatinine the alkaline reserve and the serum chlorides are usually decreased the *serum potassium and phosphorous how*ever, are usually increased particularly in cases of transfusion reaction and muscle injuries since destruction of blood or muscle releases large quantities of potassium and phosphorous

Hypertension is very common It usually appears by the third day after the initial injury and lasts until the onset of diuresis The blood pressure is most frequently at levels around 150/90 but it may go higher Slight to moderate edema invariably follows overtreatment with saline solutions so commonly employed to force a diuresis and is not really part of the syndrome consequently edema should not be a complication *with proper treatment*

The principle cause of death during the oliguric stage is uremia The typical manifestations of uremia—drowsiness coma twitchings—appear during the last two to three days of life convulsions are uncommon except in those patients who have been overhydrated, vomiting, a distressing symptom leads to further derangement of *the electrolyte pattern of the blood* The

* See Chapter 50

† See also Chapter 45

* See Chapter 48

first evidence of cardiac enlargement or pulmonary edema If the latter is severe, oxygen under pressure and phlebotomy may be life saving measures

Dialysis In the more severe cases which fail to respond to the above conservative management, or in those patients in whom treatment has been ill advised, some form of dialysis will be necessary to tide the patient over until spontaneous diuresis occurs Gastric and intestinal lavage are of questionable value and are not without danger Continuous peritoneal lavage has been employed successfully in a number of patients but is needlessly complex as compared with the intermittent peritoneal lavage recently described by Grollman The artificial kidney is a valuable instrument It effectively removes nitrogenous wastes and corrects electrolyte distortions, it is particularly valuable in the presence of hyperpotassemia Unfortunately it is not available in most hospitals since it is a complex apparatus which requires a skilled staff to operate

The most practical method of dialysis yet devised—one that is available to every hospital—is the intermittent peritoneal lavage of Grollman The technic consists of the insertion of a trocar into the anterior abdominal wall, placing a polyethylene plastic tube through the opening and removal of the trocar The omentum does not adhere to the plastic tube, which is allowed to remain in situ throughout the procedure The tube is connected alternately to a rubber drainage tube and to an infusion bottle

The irrigation fluid contains 5 77 Gm of sodium chloride, 0 25 Gm of calcium chloride 0 10 Gm of magnesium chloride and 3 Gm of sodium bicarbonate per liter of triple distilled pyrogen free water Three per cent glucose is added to delay the rate of absorption of peritoneal fluid but up to 7 per cent glucose may be used where dehydration is desired To each liter of solution is added 25 000 units of sodium penicillin and 25 mg of streptomycin

The fluid is brought to body temperature and introduced by gravity into the peritoneal cavity through the polyethylene plastic tube It is permitted to remain in contact with the peritoneal membranes for two hours, after which it is drained out by connecting the plastic tube with the rubber drainage tube Two to three liters of irrigation fluid are used at a time and irrigation is performed two or more times daily A daily injection of 300 000 units of procaine penicillin is given intramuscularly as an additional safeguard against infection Strict aseptic precautions must be employed at all times

This simple procedure has proved satisfactory both in experimental animals and in human subjects Definite reduction in the elevated levels of blood urea and creatinine and correction of the abnormal electrolyte pattern were obtained

In the second or third week, when spontaneous diuresis occurs, new problems in treatment arise With the expanding output of urine there may be a tremendous loss of salt and water, leading to hypochloremia and dehydration Careful measurements are necessary of the fluid intake and output and of the chlorides in the serum and the urine The administration of large quantities of water (5–10 liters per day) and salt (20–40 Gm per day) may be called for The total daily intake of water required is determined by adding 1000 cc (insensible water loss) to the quantity of urine passed in twenty four hours The daily requirement of sodium chloride is measured by the amount excreted in the urine the previous day At the end of five to seven days further recovery occurs and the patient may be permitted to regulate his own intake of water and salt The output of urine will continue to be above normal for several weeks

patients (from pulmonary edema and hypertensive encephalopathy) who might have otherwise recovered Prior to the use of parenteral fluids, patients whose only kidney was accidentally removed, or in whom both ureters were occluded survived for periods of from three to seven weeks Hence, it is necessary to restrict fluid intake so that no gain in body weight is observed Under normal circumstances the patient loses 1000 cc of water from the lungs and skin per day To this amount, may be added the quantity of urine passed during the previous twenty four hours, the total figure represents the water that the patient needs in order to maintain hydration In the presence of fever high environmental temperatures or loss of fluid from vomiting or diarrhea, the daily intake of water must be increased accordingly The patient's daily weight can be used as a guide for this purpose

Diet It is important to reduce the excretory load on the kidney therefore the diet should be high in calories as free of protein as possible and free of foods rich in potassium (particularly fruit juices) This diet aids by suppression of protein catabolism both of endogenous and exogenous origin thus minimizing the accumulation of the end products of protein catabolism (urea creatinine, uric acid phosphates sulfates and potassium) in the body fluids A high caloric intake (30 Gm per kg body weight in adults) is necessary in order to prevent endogenous protein breakdown A starving patient excretes as much as 12–15 Gm of urea in twenty four hours On a high caloric nonprotein diet this figure will be reduced to 2–3 Gm Bilaterally nephrectomized animals survived three times as long on a diet consisting wholly of carbohydrates as they did on an isocaloric protein diet

Borst introduced a daily diet consisting of 150 Gm of butter and 200 Gm of sugar which was well tolerated by some patients for as long as three weeks Other patients found this distasteful and were given a gruel containing 1 5 L. of water, 100 Gm of custard powder, 150 Gm of sugar, and 100 Gm of butter More recently a fat emulsion (lipomul-oral —Upjohn) has been used and apparently was well tolerated by patients This emulsion can be mixed with chocolate syrup to improve its flavor or it can be mixed with water and syrup for use in tube feedings From 250 to 500 cc per day of the emulsion can be given in divided doses or by continuous drip when tube feeding is employed This emulsion alone will furnish 1000–2000 calories per day If additional calories are required they may be furnished by 200–400 Gm of sugar or syrup added to the fat emulsion

Where parenteral feeding is necessary because the patient cannot tolerate oral feedings 20 per cent invert sugar in water (travert in water—Baxter) is to be preferred to dextrose The invert sugar is well utilized by the body and causes fewer thromboses of the veins Since the quantity of fluid to be administered is usually limited to about 1500 cc per day the total daily caloric intake by this method will be only 1200 calories For this reason oral feedings should be started as soon as the patient can tolerate them

Frequent estimations should be made of the serum chlorides carbon dioxide combining power and urea Where laboratory facilities permit determinations of the serum sodium and potassium should also be made Electrolytes particularly sodium, should not be added to the fluid or diet unless there is a significant change in the serum values It is preferable to permit the patient to remain in acidosis than to produce pulmonary edema by the administration of solutions containing sodium No attempt should be made to alkalinize the urine

Digitalization should be employed at the

exciting Under ordinary circumstances, dehydration is more common than water retention in uremia

Serum *sodium* may be normal in renal insufficiency but more frequently is low Since the damaged tubules are incapable of synthesizing ammonia and hydrogen ions, there is a considerable loss of sodium in the urine which is reflected in the lowering of the serum sodium

The serum *bicarbonate* is usually reduced in varying degrees This results not only from the accumulation of sulfates, phosphates, and other organic acids which displace the bicarbonate, but also to the increased loss of sodium and other bases in the urine as a result of the failure of the renal tubules to synthesize ammonia

SYMPTOMS

Practically every system of the body may be involved Often the only symptoms present may be nonspecific and consist of weakness, easy fatigability, dizziness and headaches As the disease progresses the patient may experience dryness of the mouth and throat, anorexia nausea and vomiting The latter usually occur in the morning and are not as a rule excessive Occasionally the vomiting may become quite severe and prolonged Under such circumstances there will be a considerable further loss of fluid and electrolytes Diarrhea with vague abdominal pains or actual cramps, is a late manifestation of uremia Variable amounts of blood may be present in the stools as a result of ulceration of the bowel

Neuromuscular symptoms are common Restlessness irritability and insomnia are frequently present as are fibrillary twitching of the muscles painful muscle cramps, and symptoms of latent tetany Most patients remain mentally clear until shortly before death others may show unusual drowsiness until they sink into the final coma Convulsive seizures may occur, usually as a result of hypertension but occasionally independently of it Occasionally flaccid paralysis may appear, usually secondary to a marked reduction in the serum potassium

Cardiovascular symptoms occur secondary to hypertension, severe dehydration, and hyper or hypopotassemia Thus dyspnea and palpitation on the slightest exertion and a hacking nonproductive cough may be present About one third of the patients with uremia develop a fibrinous pericarditis manifested by severe precordial pain with radiation to the shoulders and arms

The most striking *respiratory symptom* is the presence of the Kussmaul type of deep, rapid breathing produced by the severe acidosis Inflammation of the upper respiratory tract occurs and interstitial pneumonitis is not uncommonly present

The *skin* is generally dry, pruritic, and has a brownish yellow color Itching is very annoying The scratching leads to the production of excoriations eczematoid lesions and hyperpigmentation Pallor is the result of the profound anemia which is usually present in uremia Petechiae and purpura may occur as a result of an increased bleeding tendency Uremic patients seem to have an increased susceptibility to drug eruptions

Emaciation is common but this is occasionally masked by edema A normocytic, normochromic anemia, sometimes of a severe degree, is inevitably present in uremia The exact cause is unknown but it is thought to be due to depression of red cell production Hemolysis may play a lesser role in its genesis Whatever the cause, it responds only to blood transfusions or to improvement in renal function

LABORATORY DIAGNOSIS

Certain laboratory data reinforce the diagnosis of uremia The presence of nitrogen retention and impaired ability of the kidney to concentrate the urine are significant The determination of the blood urea

Uremia

UREMIA is the clinical state associated with nitrogen retention and disturbances of body water due to renal insufficiency regardless of etiology. Although retention of metabolic waste products is stressed in most definitions of uremia (the very word uremia means "urea in the blood"), there is now ample evidence to indicate that loss of salt and water and the development of acidosis may contribute as much to the clinical picture as the retention of metabolites. In other words, there are multiple renal dysfunctions in uremia.

PATHOGENESIS

The syndrome results from severe functional disturbance of the glomeruli and tubules. The disturbance may be caused by acute or chronic intrinsic disease of the kidney or it may be caused by prerenal factors such as circulatory disturbances, loss of water and electrolytes, and obstruction to the flow of urine. Frequently the renal and extrarenal factors may be present simultaneously. Whereas the former may not be amenable to treatment, the latter are, and the prompt institution of therapy may be life saving. The treatment of uremia will vary with the etiology of the renal insufficiency but the knowledge that both prerenal and renal factors exist may enable the physician to prevent the onset of prerenal azotemia and to treat the prerenal aspects in uremia of organic origin.

Retention of *nonprotein nitrogen* in the blood is brought about by reduced glomerular filtration due to organic or functional disturbances. It may also result from increased protein catabolism of exogenous or endogenous origin when it is superimposed on previously existing renal impairment. It also occurs secondarily to obstruction in the urinary tract.

Certain organic electrolytes are also retained as a result of impaired glomerular filtration. Thus the *sulfate* ion is entirely excreted by means of glomerular filtration. If the ingestion of sulfate continues (in food or drugs), the ion will be retained in the blood when glomerular filtration is impaired. In a similar fashion, *phosphates* are retained in the blood and also contribute towards the development of metabolic acidosis. The elevation of the serum phosphates results in a reciprocal reduction in the serum calcium. Hence the serum *calcium* is always low in uremia unless there is marked mobilization of calcium from bone.

Retention of *potassium* may occur in renal insufficiency but only in the presence of anuria or oliguria. As long as diuresis is present, potassium will be excreted, regardless of the needs of the body. Potassium is ordinarily excreted by a process of glomerular filtration and tubular reabsorption but if the serum level of potassium becomes abnormally high, the tubules will actively excrete potassium. Low serum protein levels may appear in renal insufficiency in the presence of prolonged vomiting, diarrhea or diuresis.

Organic acids are retained in renal insufficiency usually as a result of starvation or diabetic ketosis. This is brought about by the inability of the kidney to excrete excess acid. Their retention further contributes towards the development of metabolic acidosis.

Water may be retained when the intake of fluid is higher than the loss of water through the urine, skin and lungs. Such retention occurs in severe renal failure because the reduced glomerular filtration and tubular damage sharply reduce the amount of water the kidney is capable of

are rich in urea and creatinine A number of authorities maintain that nitrogen equilibrium may be *maintained on a daily* protein intake of 20–25 Gms but this conclusion has not been generally accepted

Salt The amount of salt ingested will *be determined by the clinical state of the* patient In the absence of edema and severe hypertension there is no point in restricting the intake of salt Indeed such restriction may be dangerous in renal failure since the renal tubules are not capable of conserving base These patients should be permitted a normal consumption of salt a minimum of 5 Gm of sodium chloride per day The dangers of too rigid a salt restriction are illustrated by the low sodium syndrome This usually occurs in patients with congestive heart failure or hypertensive disease whose sodium and chloride have been depleted by the repeated use of mercurial diuretics and rigid restriction of salt These patients develop uremia characterized by low serum sodium elevated blood urea acidosis (especially when ammonium chloride has been given) and many symptoms of uremia The syndrome may be fatal unless it is recognized early and treated by the replacement of the lost electrolytes However in the presence of edema or congestive heart failure the dietary salt intake must be restricted *

Fluid The intake of fluid should be sufficient to assure 1500–3000 cc of urine per day which delays the accumulation of nonprotein nitrogen The patient should be encouraged to drink water and carbonated beverages at frequent intervals If anorexia or vomiting develops parenteral fluids must be given early On the other hand it is dangerous to force fluids on an oliguric edematous patient in uremia when his contracted kidneys are incapable of excreting more than 800–1200 cc of urine per day

Acidosis Acidosis must be corrected The acidosis is produced primarily by two mechanisms Retention of sulfate and phosphate ions displace the weaker bicarbonate *ion and contribute towards* the development of renal metabolic acidosis The second factor is the inability of the tubules to produce ammonia and titrable acid which normally spare the fixed base from excretion This leads to the loss of sodium from the body Consumption of a high protein diet nausea and anorexia with diminished consumption of fluid and infection with the resulting increase in the breakdown of endogenous protein are additional factors in the production of acidosis

Acidosis should not be a problem until the later stages of the disease Ordinarily if the patient is maintained on a low protein high carbohydrate diet a large fluid consumption and an adequate supply of salt the homeostatic mechanisms of the body will maintain an adequate acid base balance Sometimes it becomes necessary to correct acidosis under these circumstances sodium bicarbonate or sodium citrate in doses of 2–6 Gm per day may be required. In the late stages of the disease when anorexia and nausea play a prominent role parenteral administration of fluids and electrolytes becomes necessary

Two types of fluids are available for the correction of acidosis The one first employed was a 1 3 per cent solution of sodium bicarbonate the one employed more re*cently is one sixth molar* sodium lactate The latter is more desirable since it is commercially available and is free from pyrogens The former has to be prepared by the user and *frequently causes pyrogenic* reactions The correction of the acidosis should be a gradual process since too rapid correction may lead to hypocalcemic tetany Since the patient with severe *acidosis* is usually also dehydrated and because of vomiting has a hypochloremia he should also be given parenteral fluids containing glucose and saline

* See also Chapter 19

and creatinine give more valuable information than the determination of the nonprotein nitrogen A proportional elevation of both the urea nitrogen and creatinine speaks for renal insufficiency whereas when the blood urea is elevated disproportionately extra renal factors are more likely to be responsible for the azotemia Elevations of inorganic serum phosphates and sulfates when present simultaneously are highly indicative of uremia. Changes in the acid base balance usually acidosis may be present but are not diagnostic

The *urine* in uremia is pale and has a fixed specific gravity of 1 008 to 1 012 even in the presence of oliguria Since the kidney is incapable of excreting an acid urine and since there is a loss of fixed base in the urine the *pH* will be above 6 Proteinuria is always present to a greater or lesser degree The examination of the sediment may give a clue as to etiology such as the presence of heme pigment cases found in lower nephron nephrosis or the finding of motility cells (polymorphonuclear leukocytes showing Brownian movement of the granules in the cytoplasm) seen in pyelonephritis The finding of very wide waxy or granular cases described by Addis is diagnostic of chronic renal failure Cultures of the urine are of value in revealing the presence and kind of infection in the urinary tract

TREATMENT

Every case of uremia deserves careful study and intelligent treatment Since many types of uremia are reversible and therefore amenable to treatment there is no justification for the hopeless point of view assumed towards these patients, even those suffering from uremia of organic renal disease Treatment of dehydration electrolyte imbalance, acidosis and congestive heart failure may result in marked clinical improvement without any change in the basic renal lesion. Surgical correction of obstruction may be a life saving measure Early and adequate treatment of prerenal azotemia will prevent the development of an irreversible uremia This calls for careful and frequent examination of the patient for early signs of fever, sweating and circulatory disturbances A careful daily record of fluids and electrolytes administered is essential just as it is important to record the volume of the urine, vomitus, diarrhea or aspirated gastrointestinal fluids Frequent determinations of the serum chlorides bicarbonate, sodium potassium calcium urea creatinine, and phosphates are also essential With the help of these data therapy has a rational basis and produces satisfactory results

Treatment of Chronic Uremia

The course of chronic renal insufficiency is irregular and unpredictable Many of these patients are ambulatory and can be treated in the office or outpatient department It is a remarkable fact that a number of such patients with a serum creatinine of 5 mg per 100 cc or above or a serum urea nitrogen of 50 mg per 100 cc or above are gainfully employed and lead a reasonably normal life The following principles are employed in the treatment of uremia

Diet The diet should be low in protein and high in carbohydrates and fats Such a diet reduces the excretory load on the kidneys and meets the caloric requirements of the body In order to maintain the nitrogen equilibrium the daily protein needs are calculated by allotting 0 5 Gm of protein per Kg body weight per day The quantity of protein lost in the daily urine is added to the above figure This usually results in an intake of 30–50 Gms of protein per day Whether the protein is of animal or vegetable origin seems of no consequence although Addis feels that proteins of animal origin are more harmful to the kidneys It is important for the patient to avoid soups and gravies derived from meat fish or fowl since these are extractives that

improvement in the azotemia, renal clearance, and the clinical state of the patient *

Hypertensive encephalopathy should be prevented if possible When it does occur it should be treated with sedatives and by a careful spinal tap for relief of intracranial pressure

Vomiting and Diarrhea Anorexia, nausea, vomiting and diarrhea are troublesome symptoms and aggravate the renal insufficiency by loss of fluids and electrolytes Patients should be taught to seek medical aid as soon as these symptoms appear The most effective method of allaying gastric irritability is by parenteral alimentation *Dehydration is corrected by glucose and* water The type and quantity of electrolytes administered will be determined by analysis of *the patient s serum, the patient s clinical* state, and by the volume of urine Diarrhea will require opiates and other measures More recently the artificial kidney and peritoneal lavage have been employed in the treatment of patients with severe uremia when anorexia, nausea and vomiting are the most distressing symptoms Dialysis may improve the condition of the patient sufficiently to enable him to eat with comfort

Sedation Adequate *sedation* is necessary to relieve pain, to allay fear and anxiety and to control nausea pruritis *twitching* and *convulsions* Paraldehyde despite its disadvantages is perhaps the *best sedative for use in uremic patients* since its excretion does not involve the kidney but the lungs If barbiturates are to be employed it is best to use the rapidly acting drugs such as seconal sodium and pentobarbital sodium The muscular twitchings and convulsions are best treated with intravenous calcium gluconate

Infection Infection must be prevented but if it is present, treat with antibiotics The presence of infection in the bladder or kidneys aggravates the uremic state and the increased endogenous protein breakdown puts an additional excretory *load on the kidneys The use of antibiotics* to prevent pulmonary infection in previously edematous lungs or to prevent infection in the catheterized bladder is advisable for the same reasons

When infection of the urinary tract is present, the possibility of obstruction should always be kept in mind Roentgenograms of the kidney and, if necessary, cystoscopy and retrograde pyelography should be employed Correction of such obstruction may be a life saving measure

Contraindicated Drugs. Certain drugs *are harmful and must be avoided in patients* with renal insufficiency Since acidosis is so frequently present in uremia the use of *acid forming drugs such as ammonium chloride* is contraindicated Mercurial diuretics cause a marked loss of sodium and water leading to further derangement of the chemical pattern of the blood As many uremic patients develop cardiac failure these drugs are often thoughtlessly employed to the detriment of the patient Alkalies in large doses are harmful and should be avoided In oliguric patients *potassium salts are contraindicated since* they may cause serious toxic effects Magnesium salts should be avoided since they not only cause a loss of fluid and electrolytes through their cathartic action but also produce neuromuscular symptoms that are quite disturbing

Anemia Anemia is present in practically all uremic patients It does not respond to iron liver folic acid or vitamin B_{12} The only effective method for *temporarily* ameliorating the anemia is transfusion of blood The transfusion does not necessarily improve renal function but it adds to the patient s well being Borst has shown that the transfusion of 500 cc of whole blood will not appreciably increase the excretion of urea and will not elevate the blood urea but an equivalent amount of protein given

* See also Chapter 10

Potassium The maintenance of homeostasis of potassium is quite important Hyperpotassemia rarely occurs when the daily output of urine exceeds one liter On the other hand low serum potassium levels may develop in patients with renal insufficiency who do not have an oliguria particularly after prolonged vomiting diarrhea, or diuresis or in patients who are maintained on a low protein high caloric diet The signs and symptoms of *hyperpotassemia* consist of parasthesias flaccid paralyses listlessness bradycardia and cardiac irregularities Serial electrocardiograms show tall peaked T waves arrhythmias and prolonged P R intervals With increasing concentration of the serum potassium auricular standstill occurs and this is accompanied by a biphasic QRS complex Finally cardiac arrest occurs

The signs and symptoms of *hypopotassemia* are muscular paralyses ileus and cardiac abnormalities which are best seen in the electrocardiogram and consist of flattened T waves and depressed ST segments

Accurate measurement of the serum potassium level is important for intelligent therapy The normal range of serum potassium is 3 5–5 3 mEq /liter The *treatment of hypopotassemia* consists in administering 2–6 Gm of potassium chloride or potassium bicarbonate per day Since fruit juices are quite rich in potassium they should be employed freely When the patient has anorexia or vomiting potassium chloride should be administered parenterally but caution must be employed not to inject the drug too rapidly *

The *treatment of hyperpotassemia* consists of the restriction of foods rich in potassium (proteins fruit juices gravies etc) the omission of potassium drugs the administration of hypertonic glucose solution and 10 per cent calcium gluconate solutions More recently orally ingested cation exchange resins have been employed to reduce the level of serum potassium

Calcium The serum calcium must be controlled in order to avoid undesirable symptoms When the serum phosphates become elevated the serum calcium is reciprocally reduced There is an additional loss of calcium through the poor functioning of the renal tubules As a result, hypocalcemia is a common finding in uremia unless there is increased mobilization of calcium from bone by vitamin D intoxication hyperparathyroidism or complete immobilization of the body Low serum calcium results in the production of muscular cramps which are very annoying and painful or latent tetany and fibrillary twitching of the muscles Tetanic convulsions are uncommon because of the augmented hydrogen ion concentration If the latter is corrected too rapidly *convulsions* may appear

The *treatment* consists of the administration of 1–2 Gm calcium gluconate daily If more rapid action is desired a 10 per cent solution of calcium gluconate can be given intravenously in 10–20 cc doses The calcium level of the blood may be elevated by reducing the level of serum phosphates This is accomplished by the oral administration of an aluminum hydroxide gel 30 cc four times a day

Cardiac failure either impending or actual, must be treated early since its presence aggravates the renal failure The usual measures such as rest digitalization and sedation should be employed Mercurial and purine diuretics are contraindicated The question of salt restriction presents a vexing problem Whereas its restriction is most desirable from the standpoint of the cardiac complication it may be most undesirable from the standpoint of the renal complication The decision as to the degree of salt restriction required will depend upon clinical judgment As cardiac function improves there is frequently a parallel

* See also Chapter 19

19. Water and Electrolyte Balance

JOHN A. LUETSCHER, Jr.

OUTLINES of the normal body fluids and of some important factors in the balance of water and electrolytes are presented in Tables 19 and 20 The physiologic mechanisms are discussed in connection with the treatment of abnormalities

Edema

EDEMA is visible evidence of a local or general increase in interstitial fluid This fluid is extracellular and contains sodium chloride and bicarbonate ions, in concentrations resembling those of the blood plasma The presence of edema therefore represents not only an excess of water but an excess of sodium as the chloride and the bicarbonate

Edema may be local or general and tends to occur in certain patterns indicating its etiology The first sign of edema in any site is an increase in measurement of the part involved Generalized edema is first reflected in a gain in weight These signs precede the onset of visible swelling pitting of the subcutaneous tissues and signs of effusions Congestion of the lungs with a decrease in vital capacity and dyspnea on exertion generally precedes the onset of edema of the lungs The prompt detection of these warning signs may allow the treatment of edema in an early stage and the prevention of more pronounced and troublesome symptoms

Edema may be related to certain changes in fluid exchange through the capillary blood vessels Trauma infection and allergy cause an abnormal permeability of the capillaries which results in the collection of a fluid of high protein content in the tissues or serous cavities A rise in the hydrostatic pressure in the capillaries associated with stasis and anoxia may occur in venous obstruction cirrhosis of the liver and cardiac failure Increased transudation of fluid of a lower protein concentration is seen in these conditions A lowered colloid osmotic pressure of the plasma results from diminution in the protein concentration and especially in the albumin fraction of the plasma This is a factor in the edema

orally will result in the excretion of 20 Gm of urea Apparently the blood protein given intravenously is used for tissue anabolism When available packed red cells are superior to whole blood since the same number of red cells are present in only one half the volume This puts less strain on the patient s vascular system Not more than 250 cc should be given at any one time but the transfusions can be given daily until the hemoglobin is brought above 70 per cent Needless to say both the whole blood and the packed cells should be per fectly typed and cross matched since a trans fusion reaction with its damaging effects on the kidneys would have most serious conse quences

Acute Uremia The acute exacerbation of a chronic glomerulonephritis or the superimposition of a lower nephron nephro sis on previously damaged kidneys will require that the patient be treated for acute uremia This is fully discussed under lower nephron nephrosis After the acute episode has cleared up, the patient returns to his previous regime

TREATMENT

Treatment of edema begins with the attack *on the underlying condition No attempt* will be made to deal with such measures since the treatment of the various conditions leading to edema is discussed under the appropriate subjects However, certain general principles apply to all of these situations

TABLE 20 ORGAN SYSTEMS WITH IMPORTANT FUNCTIONS IN THE REGULATION OF THE BALANCE OF FLUIDS AND ELECTROLYTES

Gastrointestinal tract

- Normal route of entry and absorption of water and electrolytes
- Failure of water and food intakes lead to dehydration, electrolyte depletion, and ketosis
- Loss of fluids from upper gastrointestinal tract involves loss of much chloride and sodium, and of smaller quantities of potassium, as well as of water
- Small bowel disease often leads to steatorrhea and *chronic depletion of calcium and potassium, as* well as fluid loss
- Chronic diarrhea of any type causes losses of fluid and electrolytes

Kidneys

- Normal site of excretion of most of water, sodium, *chloride, potassium and phosphate, as well as* many other metabolites
- Normal regulation of volume and composition of extracellular fluid
- Conservation of deficient ions and compensation for deficits
- Acidification of urine and ammonia formation to defend against acidosis
- Intoxication disease, or circulatory failure can destroy any of these functions

Lungs

- Normal site of oxygen intake and carbon dioxide elimination
- Disease may cause anoxemia or respiratory acidosis (excess carbon dioxide)

Sweat glands

- Together with lungs eliminate at least 1L of water daily, more in fever or hot environment

Bed Rest

Bed rest is an important factor in the elimination of edema The benefits of complete rest and the horizontal position depend on several factors Exercise and the *upright position, especially* if there is a concomitant fall in blood pressure, reduce the renal output of sodium Furthermore edema tends to pool in the lower extremities Under these conditions bed rest may result in a complete relief of edema

In some cases, the diuresis at bed rest may be small, and the edema may simply be distributed through the upper parts of the body This is undesirable if respiratory or cardiac capacity is impaired Such a patient may show an increase in pulmonary edema or pleural effusions which may be acutely uncomfortable or dangerous It is better to use a cardiac bed and to approach the horizontal position cautiously after the cardiac or respiratory reserve has been increased

Mechanical Removal of Fluid

Mechanical removal of edema and effusions may be desirable in an emergency or if other methods of eliminating edema fail Paracentesis of the peritoneal or pleural cavities may be very helpful if the vital capacity is much reduced Tense ascites may interfere with renal function and make the elimination of edema more difficult In a seriously ill patient some caution must be exercised in the removal of large volumes of effusion at any one time since the removal of more than 500–750 cc. from *the pleura may precipitate pulmonary* edema or circulatory collapse

The use of Southey's tubes is an efficient rapid, and safe method of eliminating a large volume of edema from the lower extremities and from the body as a whole These tubes are inserted into the subcutaneous tissues about the ankle under strict antiseptic precautions The whole area is then enclosed in a sterile dressing which is changed if it becomes wet, but otherwise *left intact except for occasional inspection* It is probably best to administer an anti

of nephrosis, cirrhosis, or any pathologic state associated with prolonged protein deficiency or excessive loss of proteins from the plasma.

During recent years it has become apparent that the failure of sodium and water excretion by the kidney is a major factor in the development of edema,* and that many of the types of edema which we have been accustomed to blame on disturbances of fluid exchange at the capillaries are in reality dependent on changes in the ability of the kidney to excrete sodium and water. Heart failure is usually associated with a reduction in renal blood flow, in the filtration of fluid through the glomerulus, and in the excretion of sodium and water. In nephrosis and in other types of renal disease associated with edema, the ability of the kidneys to excrete sodium is severely impaired so that here, too, the kidney plays a fundamental role. Premenstrual edema is the result of the action of the ovarian hormones on the renal tubule with resulting retention of sodium and water.

When renal function is so severely impaired that no urine is secreted, water may produce edema even though an excess of sodium is not present. This anomaly is possible because the kidney is unable to excrete water or to regulate the concentration of electrolytes in the body fluids. Edema due to water excess in anuria involves not only the extracellular fluids but produces edema also of the cells.

* See also Chapter 18

TABLE 19 BODY WATER
50 to 75% of Body Weight

Extracellular Fluid (15 to 20% of body weight)					*Intracellular Fluid* (remainder of body water)
*Blood plasma** (5% of body weight)		CAPILLARY WALL	*Interstitial Fluid** (15% of body weight)	CELL WALL	
Sodium	140 ± 3 mEq/L		Slightly less		Potassium 157*
Calcium	5.0 ± 0.5 mEq/L		Much less		Magnesium (?)
Potassium	4.5 ± 0.5 mEq/L		—		Sodium 15*
Magnesium	2.0 ± 0.4 mEq/L		Less		
Chloride	103 ± 3 mEq/L		Slightly more		*Phosphate* (?)
Bicarbonate	25 ± 4 mM/L				Protein (?)
Protein	16 ± 2 mEq/L		Much less		Bicarbonate 10†
Phosphate	1.3 ± mM/L		—		Chloride 4†
Sulfate	1.0 ± 0.5 mEq/L		—		
Organic acids	ca 5 mEq/L		—		
	Differences in osmotic pressure and composition related to much higher protein level of plasma			Differences in osmotic pressure related to different electrolytes as well as protein content of cells	

* Determination of electrolytes in serum expressed as milliequivalents to make units comparable.
(?) Variable.
† From Darrow, D. C.

should be cautious, and the patient should be closely observed to avoid increasing venous distention and pulmonary edema

Resins

Cationic exchange resins have recently been introduced to eliminate sodium through the bowel Such resins provide nonabsorbable acidic particles which combine with cations such as hydrogen (acid) sodium potassium and calcium When administered in the acid form for example hydrogen ions are released (producing immediate strong acidity in the fluids about *the particle)* while sodium potassium and other *available ions are taken up in* exchange The hydrogen ions are absorbed and must be excreted by the kidneys if acidosis is to be avoided The ammonium resin avoids local acidity but not general acidosis Similarly if the potassium form of the resin is administered the kidneys must excrete the added load of potassium In their ultimate effect then the resins offer the kidneys a chance to excrete an ion other than sodium which is difficult to excrete in patients with edema But if renal insufficiency prevents the normal regulation of acidity or of serum potassium, a dangerous acidosis or disturbance of serum potassium may occur The addition of an anionic exchange resin may reduce the load of acid but does not eliminate the possibility of disturbances of potassium or other cations of the body

The cationic exchange resins are used in *doses of approximately* 45 *Gm per day* divided into three doses A combination of ammonium and potassium forms is recommended The quantity *of sodium removed* is variable being less when dietary sodium is reduced and when the tendency to retain sodium is severe The resin may be used to eliminate sodium in combination with a reduced sodium intake or may be used to allow a more liberal sodium intake after edema has been controlled The mild acidosis produced by the ammonium form may potentiate the *action of mercurial* diuretics Dosage may be reduced after edema is controlled

It is best to use the resin for a period of not more than three weeks continuously omitting treatment for three to seven days between courses to allow the body to repair any deficits or excesses of cations The carbon-dioxide combining power, sodium and potassium levels in serum should be carefully followed at least twice weekly when treatment is initiated The patient should be instructed to discontinue medication if lassitude, weakness, or dyspnea develops Minor gastrointestinal symptoms *are common, but serious complaints may* force cessation of treatment In long term treatment calcium or iron deficiencies may develop these may be prevented by administration of therapeutic doses of these substances at intervals

The use of ion exchange resins for the elimination of sodium is contraindicated in renal disease with impaired function

Restriction of Water Intake

Water intake usually does not need to be greatly restricted and in some patients may be increased with benefit Severe water restriction is very uncomfortable leading to great thirst and to a depression of urine volume and of renal efficiency and in addition may be dangerous to the patient with chronic nephritis Severe water restriction *should be imposed only temporarily in an* acute emergency such as pulmonary edema

Moderate restriction of fluid intake is indicated when the kidneys are unable to *excrete water in normal* amounts The most striking example is the anuric patient who has temporarily lost his main channel of water excretion *If an anuric patient* is given more than 1500 cc of fluid each day and if he does not eliminate this fluid through excessive perspiration *vomiting* or diarrhea the excess of fluid simply accumulates in his body and produces edema

biotic to prevent local infection If the drainage becomes very slow or if there are any symptoms or signs of a local infection, the tubes should be removed at once Drainage is conducted from the metal tube through a light sterile rubber tube to a sterile bottle With these precautions, the chances of infection are minimal, and a large volume of fluid may be removed very efficiently

Reduction of Sodium Intake*

Reduction of sodium intake offers a simple and efficient attack on edema of many types *The principle of this therapy depends* on the tenacity with which the undamaged kidneys maintain a constant concentration of sodium in the extracellular fluids When the kidneys ability to excrete sodium is impaired by disease sodium is retained in the body if the patient continues to take in a normal amount of salt Fluid is retained with this salt so as to keep the concentration of the electrolytes in the body fluids constant If the intake of sodium can be reduced below the level which the kidney can excrete the accumulation of sodium can be eliminated and with it goes the edema fluid

The level to which the sodium intake must be reduced depends on the severity of the defect in sodium excretion In some patients the simple elimination of added salt and of obviously salty foods is sufficient In other patients it may be necessary to cook foods without salt which results in an unpalatable diet but also in a substantial reduction in the amount of salt in the food Finally for the most stringent *salt restriction it is necessary* to eliminate virtually all food containing sodium This severe restriction of sodium intake demands the elimination of practically all milk eggs baker s bread salted butter and other items of the normal diet Such severe dietary restrictions should be imposed only if the situation demands the ultimate in sodium elimination

The ability of the kidneys to excrete sodium may be so small that little fluid is eliminated If diuresis does not follow, the salt free diet can be looked upon only as a measure for preventing the development of more edema The use of such diets must often be combined with other forms of treatment designed to eliminate the accumulated fluid

Sodium Depletion Syndrome

It must be remembered that if the kidneys *are unable to maintain a normal sodium* concentration in the body fluids, the use of severe sodium restriction may result not in the elimination of fluid but rather in a reduction in the sodium concentration of the extracellular fluid This is particularly likely to happen in patients with chronic nephritis and renal insufficiency Reduction in the serum sodium concentration is also possible in patients with normal renal function who are maintained on sodium free diets over prolonged periods This reduction in electrolyte concentration leads to specific symptoms Weakness lassitude anorexia nausea muscular cramps, a fall in blood pressure more or less dehydration without thirst, and impaired renal function may ensue These symptoms are promptly corrected by the addition of sodium chloride to the diet or in an emergency by the intravenous infusion of isotonic solutions of sodium chloride but such solutions may seriously aggravate the condition for which elimination of sodium was prescribed (e g, heart failure) The least amount of sodium chloride which relieves the symptoms and signs is used If edema is present, there may be some advantage to the use of hypertonic saline solutions (2–5 per cent) but the patient s fluid intake must be sharply restricted since hypertonic solutions cause thirst The intravenous administration of such solutions

* See also Chapters 10 15 and 32

Potassium

Potassium as the chloride or nitrate, has also been used as a diuretic It is potentially more dangerous than the acidifying salts since appreciable retention in the blood will occur if there is impairment of renal function and especially if only a small volume of urine is being secreted Potassium poisoning results in a sudden onset of muscular weakness and cardiac failure Potassium salts are not particularly efficient diuretics For these reasons they are little used, but may be given in enteric coated tablets in a total dose of 5–10 Gm per day

Mercurial Diuretics*

The mercurial diuretics act by blocking the renal tubular reabsorption of sodium They are the most potent diuretics available in most cases Toxicity is uncommon but may be severe especially in cases with pre existing renal disease In such patients the urine should be watched closely, and the use of mercurials must be abandoned if diuresis fails to appear or if signs of renal irritation or decreased function result The prolonged and repeated use of large amounts of mercurials may result in the appearance of renal injury stomatitis or colitis An occasional sudden death apparently due to hypersensitivity occurs after the intravenous injection of a mercurial diuretic In spite of these contraindications the efficiency of the mercurials is such that they are widely used in all types of edema not associated with renal damage

Intramuscular injection is now preferred to the intravenous route Meralluride injection (mercuhydrin sodium) and mercaptomerin sodium (thiomerin sodium) are less likely to produce local irritation after intramuscular injection than mercurophylline injection (mercupurin mercuzanthin) or mersalyl and theophylline injection (salyrgan theophylline) A test dose of 0 5 cc is usually given on the first day, and subsequent doses may be increased to 1 to 2 cc, depending on the results Preparations of enteric-coated tablets for oral use are also available but they are generally considered less effective than injections Suppositories may produce severe rectal irritation and are not recommended Full doses of the injectable preparation are usually not given more than three times in any week, although this rule may be modified in unusual cases For use over weeks or months it is probably best to reduce the frequency of use to once a week if possible Some patients tolerate larger doses but if they are used, a watch should be kept for signs of cumulative toxicity

The use of acidifying salts for a day or so before the mercurial is administered is generally thought to increase the efficiency of the mercurial although there are some dissenting voices If relief of congestive failure is urgently required, the mercurial should be given without delay for pre treatment

The prolonged or heavy administration of a mercurial diuretic may result in a depletion of the body sodium with symptoms described above in connection with a salt free diet

Xanthines

Xanthines are most effective in cardiac edema but are not as dependable as the mercurials Toxicity however, is considerably less than the mercurials and the only difficulty is gastric irritation after full doses Caffeine is not used because of its side effects on the central nervous system Theobromine alone or as the sodium salicylate sodium acetate or calcium acetate is used in doses of 0 6–1 0 Gm three times a day Theophylline alone or as the sodium acetate calcium salicylate or ethylene diamine complex is used in doses of 0 1–0 2 Gm three times a day

* See Chapter 10

both within and without the cells With the onset of anuria the patient should receive adequate amounts of blood, plasma, or fluids to eliminate shock and to restore the renal circulation to a normal condition. Once this end has been achieved the continued forcing of fluids in the face of an established anuria is actually dangerous producing circulatory failure if it is continued too long

When oliguria does not respond to the forcing of fluids it may also be necessary to keep the fluid intake down to approximately 2 L a day This inability to excrete water is much less frequently observed than the inability to excrete sodium It occurs only in the most severe cases of cardiac failure cirrhosis nephritis and other rarer causes

If there is no impairment of water excretion it may be advantageous to give larger quantities of water in order to increase the elimination of sodium If the patient can excrete 2 2.5 L of fluid per day considerably more sodium may be washed out with the excess of water than with a smaller urine volume There seems to be little advantage gained in forcing fluids above this level

Catharsis and sweating are very trying for the patient and remove only very limited amounts of fluid They are seldom used today

DIURETICS*

When the underlying cause of the edema is satisfactorily treated the excess of fluid is rapidly excreted by the kidneys When the basic condition cannot be effectively attacked the kidneys can be induced to release some sodium and water by the use of an appropriate diuretic A most important example occurs in cardiac failure in which the proper use of a diuretic relieves the heart of the burden of a great excess of fluid and may break the vicious circle of increasing load and decreasing efficiency of the heart In disease of the kidneys, however, diuretics may be ineffectual or actually harmful If the concentrating power of the kidneys is gravely reduced or if other signs of renal failure are apparent, the use of diuretics is contraindicated unless a desperate need exists to justify the risk

* See also Chapter 10

Osmotic Diuretics

Osmotic diuretics act by increasing the elimination of water Urea may be given by mouth in doses of 40–100 Gm per day, divided into several doses The taste of concentrated solutions is very unpleasant and should be masked with fruit juices or syrup of acacia The whole usefulness of administration is lost if the patient drinks much fluid, since the extra fluid will diminish the amount of body water which would otherwise be excreted

Concentrated glucose solutions may also act as a diuretic if used in a similar manner with large doses and restricted fluid intake The efficiency in removal of edema is usually slight

Acidifying Salts

Acidifying salts and other salts foreign to the body may also be used to eliminate edema The acidifying salts are ammonium chloride ammonium nitrate and calcium chloride These salts act by presenting the kidneys with a load of acid excretion which necessitates the excretion of base For several days the kidneys may eliminate moderate amounts of sodium but subsequently the base is largely furnished by ammonia manufactured in the kidney The effect of the acidifying salts is therefore usually temporary If the kidney function is depressed more or less acidosis is produced, so that the carbon-dioxide combining power of the blood should be checked if these salts are used for more than a few days Any of the acidifying salts may be given in doses of 6–12 Gm per day in divided doses after meals The salts tend to be quite irritating to the stomach and are best given as enteric coated tablets

saline solution should be given until the blood pressure reaches normal levels and the hematocrit falls to its usual level Many chronic states of dehydration are accompanied by malnutrition with shrinkage of the circulating plasma protein When such patients are given large volumes of isotonic saline solution they may not show the expected improvement of the circulation or the plasma protein may be so depleted that hypoproteinemia and edema appear Such patients should be given plasma albumin or a similar blood substitute if the hematocrit is high or they may receive whole blood if the hematocrit is low These measures usually suffice to restore the circulation to normal within a few hours The administration of saline should be continued until the patient shows a return of normal moisture and turgor of the skin, and moist mucous membranes

It is difficult to prescribe exact amounts of saline solutions necessary to achieve optimum hydration since this will depend on the severity of the dehydration In general between one and five liters of isotonic saline solution will accomplish the desired hydration Caution must be used in the administration of large volumes of saline to patients with known or suspected disease of the heart or kidneys or with a long history of severe malnutrition It is advisable to rehydrate these patients slowly and cautiously with a constant watch for increased venous distention cardiac enlargement tachycardia, or pulmonary distress or edema

When adequate rehydration has been completed the patient may receive on subsequent days enough isotonic saline to cover his daily losses through skin bowel and kidneys It is unwise and unnecessary to give very large amounts of saline solutions daily over any period of time without considering the possibilities of accumulation with edema and cardiac strain or of potassium depletion

Water must be supplied in adequate quantities to insure a good urinary output over and above the amounts of fluid which are necessary for rehydration This water can be advantageously combined with the glucose which is necessary to supply calories and to suppress excessive protein and fat breakdown Gamble's studies have shown that 100 Gm glucose per day, given with 1200 cc water, will allow a normal man to survive with a minimum of sacrifice of body fluids and of protein breakdown If there is excessive loss of fluid through perspiration or other losses the volume of fluid can be increased The best guide in the presence of normal kidneys is the urine volume, which should be maintained above one liter a day and preferably in the neighborhood of 1500 cc

If the patient is malnourished or if intravenous feeding must be continued for more than a few days supplements of vitamins protein (as blood plasma or protein hydrolysate) and other electrolytes (potassium calcium) should be added to bring the intake up to a minimum necessary for maintenance and repair This therapy is costly and tedious to prepare and administer and should be altered suitably as soon as the patient is able to take any or all of his food by mouth

If a patient suffers from dehydration circulatory collapse, hemoconcentration and mild renal failure without evident cause or following a mild infection or trauma if he fails to respond to the usual measures for rehydration, or if he shows a low concentration of sodium and chloride in the serum the possibility of hypoadrenalism must be considered *

Potassium Depletion

Potassium depletion occurs when potassium intake in food or fluids is absent for many days, or when excessive loss of potassium has taken place for example in the

* See Chapter 50

Dehydration and Electrolyte Loss

DEHYDRATION may occur whenever excessive quantities of body water or electrolytes are lost Fluid and salt intake may be blocked by nausea and vomiting or may simply fail when the patient is too ill to desire or obtain his usual quota of fluids and food The normal individual obtains about two thirds of his fluid intake from water and other fluids and about one third from the water content and water of combustion of his food He normally loses about one liter per day in evaporation from the lungs and skin The rest of the fluid is excreted in the urine with a very small amount in the stool Excessive water loss may occur from vomiting, diarrhea drainage from intestinal tubes and fistulae excessive perspiration during fever or exposure to heat or unusual loss through the kidneys

Dehydration from lack of water is accompanied by some loss of electrolytes but the concentration of salt in the body remains high enough to produce thirst When sodium or chloride is lost in large amounts the concentration of electrolytes in the body declines so that dehydration may occur without appreciable thirst Significant losses of sodium or chloride produce dehydration even though a normal water intake is maintained Moreover depletion of body sodium leads to hemoconcentration and impairment of the circulation and of renal function which are more severe than those observed in water deprivation

When the kidneys are injured their reaction to loss of body water and electrolytes is often abnormal and the usual conservative and stabilizing actions are impaired Since under these conditions many of the usual rules break down much closer observation of the state of hydration and of the chemical composition of the blood is usually necessary to determine the proper treatment In patients with renal insufficiency or severe heart failure for example the concentrations of sodium and chloride in the extracellular fluid may be much reduced with or without appreciable dehydration and not infrequently in the presence of edema Prompt detection of electrolyte depletion in such cases requires regular chemical analyses of blood The chloride content of the urine is a useful index of the adequacy of salt intake in patients with normal kidneys but a low urine chloride may be seriously misinterpreted in the presence of renal or circulatory failure associated with impaired excretion of sodium and chloride when the administration of sodium chloride is contraindicated

The clinical syndrome of sodium depletion which may occur during a sodium elimination program in the treatment of edema has been previously described (see Sodium Depletion Syndrome)

In the past dehydration has usually been treated primarily by replacement of extracellular fluid During recent years more has been learned about depletion of intracellular water in which potassium is the chief basic ion The observation of changes in the intracellular fluids is difficult and the replacement of potassium carries certain risks not encountered in the use of solutions of sodium salts Nevertheless the prevention detection and treatment of potassium depletion are important and may occasionally be necessary to save life

Treatment of dehydration requires the replacement of water and sodium chloride losses and subsequent supply of daily needs Replacement with isotonic solution of sodium chloride should be based on the state of hydration of the patient The circulation deserves the most immediate attention and

if the infusion is supplying either inadequate or excessive amounts of potassium The electrocardiogram usually allows rapid differentiation between the clinically indistinguishable forms of paralysis caused by deficiency and excess of potassium The exact status should be defined at least twice daily by serum potassium determinations

Potassium Intoxication

MUSCULAR paralysis, including respiratory failure, and disturbances of cardiac function appear when the level of potassium in the serum rises above 8–10 mEq /L (32–40 mg per 100 cc) This situation occurs spontaneously in patients with renal failure, especially after prolonged anuria due to acute renal injury (lower nephron nephrosis) * It may appear after the administration of potassium, after trauma or surgery, or after the administration of ACTH or cortisone, in patients whose kidneys are unable to eliminate the extra load

The electrocardiogram offers a simple method for distinguishing potassium intoxication from the closely related clinical picture of potassium deficiency When the serum potassium is too high, the T waves become high and peaked, the QRS complex is broadened (intraventricular block), and finally the record takes on a bizarre pattern resembling ventricular tachycardia or fibrillation The P R interval may be prolonged or the P wave may disappear The physiologic disturbance may become clinically evident as irregularity of cardiac rhythm cardiac failure or slowing and terminal cardiac arrest occur at high serum potassium levels

The treatment of potassium intoxication is directed toward three ends First the intake of potassium should be stopped Then temporary, quick methods of lowering or antagonizing the extracellular potassium level should be used Intravenous infusion of saline or glucose solutions and the administration of insulin may produce some lowering of the serum potassium Intravenous calcium gluconate solution (1 Gm in 10 cc) may counteract some effects of a high serum potassium Finally efforts may be made to eliminate potassium from the body by dialysis (artificial kidney or intestinal or peritoneal dialysis) if the situation is urgent, or by the use of a potassium free ion-exchange resin by mouth or by enemas in a total daily dose of 50 Gm, divided into two to four doses

* See also Chapter 18

Calcium and Phosphorus

CALCIUM

Calcium is important not only as an essential part of bone, but also as a necessary element of the extracellular fluid in the regulation of neuromuscular activity The control of the serum calcium is accomplished by the balance of calcium absorption (diet vitamin D, gastrointestinal function) against calcium exchange with bone and its elimination in stools and urine, which involve parathyroid and renal function Since a large amount of circulat

gastrointestinal secretions in the urine in acidosis or with a high level of adrenal cortical steroids (stress, overdosage with ACTH or cortisone) The serum potassium is not necessarily low in such situations especially if the function of the circulation or kidneys is impaired For example a patient with diabetic acidosis may initially have a high serum potassium it is usually only after some hours of treatment that the serum potassium falls to the lowest levels A rapid decline in the level of the serum potassium may follow the intravenous administration of solutions of glucose or of sodium salts in a depleted patient Insulin lowers the serum potassium while calcium salts may precipitate symptoms of potassium deficiency by its physiologic antagonism

The patient depleted of potassium may show generalized weakness and apathy If the serum potassium falls below 3 mEq /L (12 mg per 100 cc) there may be symmetrical muscular paralysis sometimes ascending with loss of deep tendon reflexes Respiratory or cardiac failure may result in death The recognition of this syndrome is imperative since it is entirely reversible if proper amounts of potassium salts are administered When it is *not* possible to obtain a serum potassium quickly enough to be helpful a presumptive diagnosis can usually be made from the electrocardiogram The characteristic changes include depression (sagging) of the S T segment and lowering or inversion of the T waves The Q T interval is prolonged A prominent U wave may follow the T wave The P R interval may be prolonged The appearance of changes in the S-T segments T waves or Q T interval especially if a previous record is available for comparison is highly suggestive of hypopotassemia and justifies treatment in an emergency The serum potassium should be determined to make a specific diagnosis

If the patient is not too ill the administration of potassium salts by mouth is effective and safe Potassium chloride 3 Gm dissolved in flavored water or fruit juice can be given by mouth and repeated as the clinical situation indicates It is probably best not to give more than 10 Gm of potassium chloride per day without electrocardiographic control or chemical analysis of the blood to guide the treatment but doses should be continued over a period of several days to avoid a recurrence of symptoms *Potassium salts should not be given to patients with circulatory collapse, oliguria or renal insufficiency,* unless the serum level is dangerously low and unless facilities are available for accurate supervision of treatment

In a serious emergency a solution of potassium chloride may be given intravenously Before potassium is given intravenously it should be known that the patient has a low serum potassium and that he has none of the contraindications of shock oliguria or renal insufficiency If the intravenous use of potassium seems absolutely necessary 3 Gm * of potassium chloride dissolved in 1 L of water (0 3 mg per 100 cc or 40 mEq /L.) should be given by a slow intravenous drip until the clinical symptoms and the electrocardiographic abnormalities associated with a low serum potassium have been eliminated The infusion should then be stopped and further treatment carried on by oral doses of potassium as previously outlined. If the patient is unable to take medication by mouth a continuous infusion containing potassium chloride 0 3 per cent should be administered at a rate sufficient to introduce about 10 Gm potassium chloride in the first twenty four hours Treatment on subsequent days should include a least 3 Gm of potassium chloride daily Close clinical observation is essential to detect weakness or loss of tendon reflexes which may occur

* Average adult dose Dosage should be reduced on a basis of body weight in children or smaller individuals

Acidosis and Alkalosis

ACIDOSIS

Acidosis results when the kidney is unable to excrete all of the acid metabolites at a rate equal to their production. This imbalance may be due to an excessive production of acid, as in diabetic acidosis, or it may be due to impairment of renal function. In either case abnormal amounts of sodium are lost from the body with a resulting decrease in the sodium and bicarbonate concentrations of the blood.

If the acidosis is very severe as indicated by a carbon-dioxide combining power of the blood below 12 mEq/L. (25 volumes per 100 cc.) sodium lactate or bicarbonate solution may be administered intravenously. It is rarely necessary to give great volumes of these solutions if treatment is directed toward the reduction in the excessive load of acid. Sodium lactate is usually given as a 1/6 molar solution in a dosage of 500–1000 cc. Sodium bicarbonate solutions (1–2 per cent) have the same effect, but must be sterilized in sealed glass ampules to avoid loss of carbon dioxide.

When the acidosis of nephritis is rapidly corrected by the injection of alkaline solutions, the appearance of tetany may require the addition of calcium salts to the infusion or the use of sodium chloride instead of the more alkaline salts. This situation may occur in patients with a low serum calcium concentration when tetany may be suppressed by the acidosis and brought out by the administration of alkaline solutions.

As soon as possible the excess load of acid should be removed by attention to the factors producing acidosis. Adequate carbohydrate in starvation or the administration of insulin and glucose in diabetes will stop the overproduction of ketone ds. The physician should be sure that acidosis is not produced by some acidifying salt which prescribed perhaps as a diure phritis, some benefit may follow in the protein content of the the administration of small daily alkalies (calcium carbonate and al hydroxide may be preferable to so carbonate if edema is present). Som acidosis is due to loss of basic sec from the biliary or intestinal tract quate replacement of sodium bicarb should remedy this situation.

When acidosis occurs in a patient normal kidneys it is usually accompan by dehydration, which should be trea as described above. When the renal fu tion is impaired either dehydration edema may exist in the presence of acidosi

In the metabolic types of acidosis the excess of acids accumulate in the blood and reduce the carbon dioxide combining power. Partial respiratory compensation of blood neutrality is achieved by deep slow respiration. When acidosis is caused not by these fixed acids but by an accumulation of carbon dioxide due to disease of the lungs, the carbon-dioxide combining power of the blood is increased. No special treatment is required for this respiratory acidosis, which is best treated by attention to the basic pulmonary disease.

ALKALOSIS

Alkalosis may result from loss of acid secretions from the body or from an excessive intake of alkali. When large volumes of acid (chloride) secretion are lost from the body as in pyloric obstruction the alkalosis is accompanied by dehydration and should be treated with isotonic saline solutions in adequate volume to meet the loss and to supply some extra sal

ing calcium is bound by the blood proteins the serum protein level must be known before the serum calcium can be interpreted It is useful also to know the serum inorganic phosphorus level and the alkaline phosphatase activity In the presence of normal kidneys the height of the serum calcium can be inferred from the urinary calcium quickly and easily estimated by Sulkowitch s test *

Hypercalcemia

Abnormally high levels of serum calcium result in weakness anorexia constipation polyuria an increased incidence of renal stones and calcification of the kidneys and of other tissues Treatment is directed toward removal of the causative factor whether this be an excessive intake of calcium or vitamin D or a rapid breakdown of bone by atrophy metastatic cancer or hormonal stimulation (hyperparathyroidism) The forms of hypercalcemia associated with hyperglobulinemia should be differentiated

Hypocalcemia

Lowered serum calcium levels may lead to tetany or to failure of normal growth and calcification of bone Deficient intake of calcium or of vitamin D or impairment of gastrointestinal absorption causes rickets or osteomalacia and occasionally tetany In such cases the Sulkowitch test shows absence of calcium from the urine These patients are treated with adequate amounts of readily absorbable calcium salts (chloride or lactate) and vitamin D to raise the serum calcium and phosphorus toward normal The upper limit of dosage is often determined by gastric irritability and absorption If osteomalacia is present the serum level may continue to be subnormal despite heavy treatment until the bones finally become recalcified

In other cases calcium is being lost through the kidneys for example in chronic metabolic or renal acidosis The Sulkowitch test is strongly positive If calcium is being lost due to chronic acidosis Shohl s mixture of sodium potassium and calcium citrates may be used provided renal excretory function is normal (watch for edema or potassium intoxication) In the low serum calcium of chronic renal disease associated with uremia treatment is difficult and usually unnecessary since acidosis and the low blood proteins minimize the likelihood of tetany

Hypoparathyroidism is a rare cause of low serum calcium occurring spontaneously or after injury to the parathyroids during thyroid surgery It is most easily treated with calcium salts and vitamin D

PHOSPHORUS

Serum inorganic phosphorus is closely linked with calcium by their tendency to precipitate in combination An excess of either ion is likely to reduce the amount of the other ion absorbed and dissolved in the body fluids Combined deficiencies exist in rickets and osteomalacia Acidosis with good renal function also tends to deplete both ions Treatment is generally directed toward replacement of calcium but a normal intake of phosphorus should be maintained

A high serum phosphorus with lowered serum calcium occurs in uremia (and in hypoparathyroidism see above) Some reduction of phosphorus may follow the use of aluminum gels (20–40 Gm per day) with calcium lactate Modest elevations of the serum phosphorus occur during normal childhood and in acromegaly

A low serum phosphorus with elevated serum calcium is seen in hyperparathyroidism and in rare patients in whom massive quantities of calcium are absorbed from the gastrointestinal tract or released from bone The treatment is that of the underlying condition

* See Chapter 49

20. Diseases of the Nerv[ous] System

I. Infectious, Neuritic, and Degenerative Diseases

SIDNEY CARTER
& H HOUSTON MERRITT

MANY of the disorders of the nervous system which once led to early incapacitation or death, can now be arrested, controlled or cured There are still some diseases particularly those of the degenerative group, which are therapeutically inaccessible but even in these conditions modern research and increasing knowledge are making new therapeutic agents and methods available With the use of present day therapy the physician has much to offer patients with diseases of the nervous system

Bacterial Infections

THE MENINGITIDES

Acute Purulent Meningitis

Although any of the pathogenic organ[i]sms can produce meningitis the most [c]ommon causes are the meningococcus [pn]eumococcus streptococcus *Hemophilus [in]fluenzae*, and staphylococcus The clinical [pic]ture is essentially the same in all infec[tion]s and consists of severe headache, vomit[ing] irritability clouding of consciousness [whic]h may reach deep coma and mental [confu]sion The patient is usually acutely ill and may be restless irrational and uncooperative There is stiffness of the neck and Kernig's sign The reflexes may be depressed or hyperactive and there may be a bilateral Babinski response Focal neurologic signs are infrequent The temperature in the beginning may be normal but it usually becomes elevated later to between 101° and 103° F, and the pulse may be either slow or rapid

The diagnosis is made by examination of the cerebrospinal fluid and the [...]

necessary functions Potassium depletion is common in such patients and may lead to intractable alkalosis or muscular weakness (see Potassium Depletion')

When alkalosis is due to an excessive intake of sodium bicarbonate or related salts (Sippy powders) the state of hydration is usually normal The symptoms in such patients may result either from tetany vicarious calcification or secondary renal failure In any case the immediate need is to recognize the origin of the trouble and to eliminate excessive intake of alkalies If tetany is a problem the intravenous injection of isotonic saline is more rational than the intravenous use of calcium salts since the serum calcium is usually normal in these conditions while an excess of calcium may lead to further abnormal deposition of calcium in the tissues Acidifying salts may be given by mouth Fortunately the bad effects of precipitation of calcium in the renal tubules and elsewhere in the body are usually reversible if the situation is recognized

The metabolic types of alkalosis which have just been described are associated with an increase in the carbon dioxide combining power of the blood Some nervous persons and an occasional patient with organic disease of the brain may show a chronic type of hyperventilation which results in tetany During an episode of hyperventilation the patient feels numb, tingling light headed sometimes mildly nauseated and apprehensive If the overbreathing is carried further the characteristic muscular stiffness and cramps of tetany may develop This situation is due to excessive loss of carbon dioxide from the blood but unless it is very severe and repeated the carbon dioxide combining power of the blood is not affected The patient may be relieved by rebreathing air from a paper sack or by inhalation of oxygen containing 5 per cent carbon dioxide If the patient is sensible enough to understand the reassurances that his symptoms are simply due to overbreathing he may be able to break the habit and have no further trouble Many of these patients require some psychiatric attention to the anxiety state or other psychic disturbance which brings on the hyperventilation A similar type of alkalosis due to hyperventilation may occur during the first few days at high altitudes especially when exercise is attempted The symptoms are relieved by the inhalation of oxygen

A drug fever may appear in the first week of treatment and it may be difficult to determine whether the fever is due to the drug or to a recurrence of the infection Other evidence of drug toxicity such as a rash is helpful in distinguishing the two The cause of the fever can be accurately determined by examining the spinal fluid

Penicillin Therapy Penicillin is not considered to be as effective as the sulfonamides in the treatment of the uncomplicated case of meningococcic meningitis It is indicated, however, in those patients with the fulminating form of the disease when it is given in addition to the sulfonamides, and in cases refractory to the sulfonamides or when complications prevent the use of sulfonamides

The usual parenteral dose of penicillin is 50 000 to 100 000 units every three hours The intrathecal dose is 15 000 units dissolved in 10 cc of sterile physiologic saline injected once daily However, recent evidence has shown that when sufficiently large amounts of penicillin are given parenterally there is no need for its intrathecal use It should, therefore, be given intramuscularly in large doses of 1 000 000 units in aqueous solution, every two hours When penicillin is used alone or in combination with sulfadiazine it is continued for the same length of time as the sulfonamide, with gradual reduction in dosage in the same manner as with the latter

Toxic reactions to penicillin are unusual Rarely, an urticarial rash with severe pruritus may occur, necessitating withdrawal of the drug The intraspinal use of penicillin should be avoided, as it may produce damage to the roots of the cauda equina or to the spinal cord

Treatment of the Fulminating Form of Meningococcic Meningitis (Waterhouse Friderichsen Syndrome) This form of the disease has a very grave prognosis and unless active measures are instituted immediately, death ensues In these cases there is usually an overwhelming bacteremia with a minimal degree of meningeal involvement Such patients have a marked elevation of temperature, an extensive purpuric rash, low blood pressure, and signs of circulatory collapse

In such cases, it is necessary to combat the shock, the adrenal insufficiency,* and the overwhelming meningococcemia An intravenous solution of 1000 cc of 5 per cent glucose in saline, 25 cc of adrenal cortical extract, and 5 Gm of sulfadiazine sodium is given immediately At the same time 10 cc of the adrenal cortical extract is administered subcutaneously Penicillin is also started immediately and continued in a dosage schedule as given in the paragraph under penicillin therapy The sulfadiazine is repeated intravenously in 2 Gm doses at eight hour intervals until the patient is able to take the medication by mouth, when the regular dosage schedule for the sulfonamides is followed The adrenal cortical extract is repeated in 10 cc doses subcutaneously every four hours and 5 mg of desoxycorticosterone acetate is given intramuscularly every six hours In addition intranasal oxygen and repeated transfusions of plasma or whole blood are given Care must be taken to prevent pulmonary edema which results from overloading the circulation

Symptomatic Therapy The fluid intake should be maintained at 3000 cc a day and the urinary output at about 1500 cc per day When insufficient amounts are taken orally, additional fluids can be given parenterally as 5 per cent glucose in distilled water or physiologic saline

In most cases sedation will not be necessary However, when the patient is restless or irrational, such drugs as phenobarbital 0 2 Gm, sodium amytal 0 2 Gm chloral hydrate 1 0 Gm, and paraldehyde 6 to 8 cc can be used The latter drug is particularly effective in patients difficult to control and

* See also Chapter 30

organism can be determined only by bacteriologic stains and by culture of the fluid The fluid is under increased pressure and is usually cloudy or frankly purulent in appearance There is a marked pleocytosis with polymorphonuclear leukocytes predominating The protein is increased and the sugar is decreased—usually to below 20 mg per 100 cc The chlorides also are reduced

Early diagnosis is important in reducing the mortality of the disease Treatment usually is much less effective when instituted late in the course of the illness Patients with meningitis should be treated in a hospital because of the necessity of many laboratory studies and general supportive measures that are needed in addition to specific therapy

The sulfonamides and the antibiotics are the drugs of choice for the treatment of infections of the meninges and this therapy has almost entirely replaced specific sera and spinal fluid drainage * Most often they are given orally or parenterally The intrathecal administration of the antibiotics is rarely indicated while the sulfonamides are never given by this route Sulfadiazine and sulfamerazine are the most commonly used sulfonamides Penicillin and streptomycin are the antibiotics that have the greatest value in the treatment of meningitis at the present time Aureomycin and chloramphenicol appear to be the most useful of the newer antibiotics particularly in the treatment of influenzal meningitis A blood culture should be taken in addition to a specimen of spinal fluid in all cases before treatment is started

Meningococcic Meningitis This is the most common of all the meningitides and occurs either in epidemics or sporadically The mortality in uncomplicated cases treated early is usually under five per cent The drug of choice is sulfadiazine or sulfamerazine Penicillin is indicated only in those cases that fail to respond to sulfonamides within forty-eight hours or when complications prevent the use of the latter drugs However, in the fulminating form of the disease both drugs should be administered together from the beginning

Sulfonamide Therapy When possible an initial dose of 4 Gm of sulfadiazine is given orally Subsequent dosage should be 1 to 2 Gm every four hours (every six hours when sulfamerazine is used) day and night so that a blood concentration of 10 to 15 mg of unacetylated drug per 100 cc of blood is maintained If the patient is unable to take or retain the medication when given by mouth, the first dose should be given intravenously as a 0 5 per cent solution of sodium sulfadiazine in sterile saline (5 Gm in 1000 cc of saline) Half this initial dose is given every eight hours until the patient is able to tolerate the medication by mouth The drug should be maintained in full dosage for four days after complete symptomatic recovery A reduced dosage (3 Gm of sulfadiazine or 2 Gm of sulfamerazine daily) should be maintained for an additional three days

Toxic Reactions of the Sulfonamides These are less common with sulfadiazine than with the other sulfonamides Gastrointestinal disturbances and dermatitis, unless severe or progressive are not indications for discontinuing the drug Urinary complications such as gross hematuria hemoglobinuria and anuria are indications for stopping the sulfonamide immediately and for substituting penicillin Such urinary complications can be avoided or minimized by alkalinizing the urine by giving sodium bicarbonate orally or a sixth molar solution of sodium lactate intravenously or by maintaining an adequate fluid intake (3000 cc daily) The drug should be stopped immediately and penicillin substituted if there is evidence of granulocytopenia Other measures such as transfusions may be indicated

* See also Chapter 4

skull and is due to a less virulent type of the organism

While streptomycin is an extremely effective antibacterial agent against *H influenzae,* its use alone in the treatment of influenzal meningitis is inadvisable because of the possible development of streptomycin resistant organisms The sulfonamides should be used in conjunction with streptomycin because they have an inhibitory effect upon *H influenzae* and because they prevent the appearance of streptomycin resistant organisms If the patient is very ill or if treatment has been delayed, type specific rabbit antibody serum should be given in addition to streptomycin and sulfonamides Rabbit serum should also be given if the streptomycin sulfonamide combination has failed to bring about an improvement within forty-eight hours

Streptomycin Therapy Streptomycin is given parenterally and occasionally intrathecally The daily dose of streptomycin is 0 25–0 5 Gm for infants and small children and 1 Gm for older children and adults This is given intramuscularly in divided doses every six hours during the twenty four hour period When streptomycin is used intrathecally it is given in one daily dose of 25 mg to infants and children and 50 mg to adults The drug is administered in 5–10 cc of sterile saline after an equal or greater amount of spinal fluid has been removed The streptomycin therapy is maintained for a period of five to seven days

Toxic Effects of Streptomycin The most serious effects are those that are due to damage to the eighth nerve and the vestibular apparatus These effects are more likely to occur in patients who have been maintained on streptomycin for more than one week It is essential to use the shortest period of treatment consistent with effectiveness

Sulfonamide Therapy The sulfonamides are administered as described above for meningococcic meningitis They should be maintained for two weeks after apparent clinical cure, as determined by the general condition of the patient and the results of examination of the cerebrospinal fluid particularly the bacterial and sugar content

Serum Therapy The potency of rabbit antiserum specific for Type B *H influenzae* is expressed in terms of milligrams of antibody *nitrogen per cubic centimeter* The size of the initial dose depends upon the amount of sugar in the spinal fluid If the spinal fluid sugar is 25 mg or less the initial dose should consist of 150 mg of antibody nitrogen A spinal fluid sugar of over 25 mg calls for 75–100 mg of antibody nitrogen The initial dose of antibody is diluted in an amount of isotonic saline equal to 10 cc per Kg of body weight and given intravenously over a period of two hours Subsequent doses are determined by assaying varying dilutions of the patient s own serum each day against a subculture of the organisms recovered from his own cerebrospinal fluid The total dose usually does not exceed 250 mg

Aureomycin Therapy Aureomycin may be given orally or intravenously depending upon the patient s state of consciousness When given orally, the initial dose is 0 75 Gm This is followed by 0 25 Gm every four hours When the patient s state of consciousness makes oral administration unfeasible, the aureomycin is given intravenously in an initial dose of 0 1 Gm followed by 50 mg every four to six hours until oral feedings are again possible Treatment is maintained for a period of ten to fourteen days

The untoward reactions of aureomycin are nausea, vomiting and diarrhea

Chloramphenicol Therapy Recent work has indicated that this antibiotic may be the most effective agent available at the present time for the treatment of influenzal meningitis An initial oral dose of 0 75 Gm followed by 0 25 Gm every four hours

in such case should be given intramuscularly Morphine and codeine are to be avoided The headache that is frequently present should be treated with 0.6 Gm of acetylsalicylic acid as necessary, or by 0.5 Gm of caffeine and sodium benzoate If medication is not effective in relieving the headache drainage of fluid by lumbar puncture may be of value Frequent lumbar punctures otherwise are not necessary or advisable An initial examination is necessary for the diagnosis and re-examinations to determine the efficacy of the therapy are usually sufficient at two- to three-day intervals

Treatment of Complications The more common complications of meningococcic meningitis are arthritis eye infections and deafness The first two usually respond to chemotherapy After an adequate trial of chemotherapy localized purulent infections should be treated surgically There is no treatment for the deafness

Prophylaxis The contacts of cases with meningococcic meningitis should be given a single dose of 2 Gm of sulfadiazine

Pneumococci Meningitis *Pneumococcus* ranks second to meningococcus as a causative agent of meningitis The meninges may be the primary site of infection by the pneumococcus but more often the meningitis is secondary to an infection in the middle ear nasal sinuses the lungs or following fracture of the skull Prior to the use of the sulfonamides the mortality rate of pneumococcic meningitis was well over ninety per cent With the use of sulfonamides and penicillin the mortality rate has been reduced to approximately wenty five per cent

Since this disease has such a high mortal y rate it is necessary to use the combined erapy of sulfonamides and penicillin in ll dosage They are given as described ove for meningococcic meningitis If atment has been delayed or the patient n coma it may be advisable to give a single intrathecal dose of penicillin in tion to the above regimen For intrat injection, 15 000 units of penicillin solved in 10 cc. of sterile physiologic sa should be injected after the removal of equal or greater amount of spinal fluid.

If necessary, the focus which gave r to the meningitis should be treated sur cally Symptomatic and supportive mea ures are the same as for meningococc meningitis

Streptococcic Meningitis This type o meningitis is usually seen in association with otitis media and mastoiditis With the increased use of sulfonamides and penicillin for upper respiratory infections there has been a decrease in the incidence of streptococcic meningitis Although any of the types of streptococcus may be responsible for producing meningitis, hemolytic streptococcus most often is the causative agent Combined sulfonamide and penicillin therapy has reduced the mortality rate of this disease from over ninety five per cent to less than thirty five per cent

Although penicillin is a more effective agent than the sulfonamides in the treatment of hemolytic streptococcus infections the mortality rate in this disease is sufficiently high to warrant the use of all effective therapeutic agents Penicillin sulfonamide therapy should be administered in the method described above for meningococcic meningitis Symptomatic and supportive measures are the same as in the latter disease

Influenzal Meningitis This type of meningitis is seen most frequently in infants and young children It is almost always a primary disease caused by Type B influenza bacillus The mortality rate of influenzal meningitis has been reduced from over 90 per cent to less than 10 per cent by the use of streptomycin aureomycin chloramphenicol sulfonamides, and rabbit anti serum In adults influenza meningitis is most commonly a sequel to fra

Intramuscular Therapy Streptomycin 1–2 Gm, should be given daily and divided into four six hour doses This dosage should be continued uninterruptedly for at least five to six months When there is the additional complication of miliary tuberculosis the treatment period should be one year The return of the sugar content to normal in the cerebrospinal fluid and the absence of organisms in smears and cultures are reliable criteria of improvement

Intrathecal Therapy Intrathecal therapy is indispensable in the treatment of tuberculous meningitis Streptomycin 50–100 mg is given in one dose daily It is recommended that the intrathecal injections be continued daily for at least eight weeks after the last positive films or cultures and until the cerebrospinal fluid shows no more cell fluctuations until the protein level is stationary or falling and until all clinical signs of active disease have disappeared

Patients who develop signs of spinal block (manometric evidence and a rapidly increasing cerebrospinal fluid protein) or of increased intracranial pressure should have burr hole trephination by a neurosurgeon The increased pressure can then be relieved by ventricular taps Streptomycin usually in half the intrathecal dose, can be injected daily into the ventricles through these burr holes until the lumbar subarachnoid space opens again

Used alone *p* aminosalicylic acid is not particularly effective in the treatment of tuberculous meningitis When given concomitantly with streptomycin, it serves to decrease or delay the appearance of streptomycin resistant tubercle bacilli The daily dosage is 12 Gm given in the form of the solution of the sodium salt three times a day with meals Some of the undesirable side effects of *p* aminosalicylic acid are skin eruptions and such manifestations of gastrointestinal irritation as anorexia nausea vomiting and diarrhea

Promizole has been combined with streptomycin in some studies and favorable results have been reported In one series in which there was a survival rate of 76 per cent, the promizole was given by mouth four times a day in amounts sufficient to produce concentrations in the blood of 1–3 mg per 100 cc This usually required from 1–8 Gm daily

Cairns and his co workers have given tuberculin (purified protein derivative) intrathecally in an attempt to produce lysis of the exudate and thus permit streptomycin to act more effectively While the results were striking in some of their cases it is still too early to evaluate the results of such therapy

ENCEPHALITIDES (BRAIN ABSCESS)

Brain abscesses usually are secondary to fractures of the skull, extension of a focus of infection in the middle ear, mastoid or nasal sinuses, metastasis from lung abscess bronchiectasis, endocarditis, or infection in the abdominal cavity or extremities Almost any of the common pyogenic organisms may be the causative agent of the brain infection The symptoms of a brain abscess may be caused by increased intracranial pressure, localization of the abscess to some one part of the brain (focal symptoms) and infection The cerebrospinal fluid is under increased pressure and the protein level is elevated Cells frequently are present and the sugar content usually is normal

Adequate treatment with antibiotics and chemotherapy of the sources of infection outside the nervous system has greatly reduced the incidence of brain abscesses * If a brain abscess occurs, as result of a metastasis or extension of the infection despite prophylactic treatment or because of failure to treat the source of infection it should be treated in a hospital by a competent neurologic surgeon

There are no entirely satisfactory criteria

* See also Chapter 4

will maintain an adequate blood and spinal fluid concentration The rectal administration of 500 mg in capsule or suppository form will enhance the orally administered drug Treatment is maintained for a period of eight to ten days

The toxic effects of chloramphenicol are nausea vomiting skin eruptions and more rarely severe neutropenia

Staphylococcic Meningitis This form of meningitis is less frequent than the types lready described It usually occurs second ary to infections of the paranasal sinuses mastoids and vertebrae or as a complication of a staphylococcic bacteremia Penicillin is the drug of choice and should be given in the dosages described under meningococcic meningitis Combined penicillin sulfonamide therapy can be used to advantage Treatment should be maintained for two to three weeks after the meningeal infection has subsided It may be necessary to remove the primary focus by surgical drainage to prevent recrudescence of the meningitis

Colon Bacillus Meningitis Colon bacillus is a relatively frequent cause of meningeal infection in children under the age of 1 year The treatment is with streptomycin or streptomycin and sulfonamides as outlined under influenzal meningitis

Meningitis Due to *Pseudomonas aeruginosa (B pyocyaneus) Klebsiella pneumoniae* and *Aerobacter aerogenes* The men ngitides produced by these gram negative organisms are rare For the most art they respond to combined streptomycin sulfonamide therapy or to aureomycin as described under influenzal ningitis

berculous Meningitis*

berculous meningitis is always second to tuberculosis elsewhere in the body onset of meningeal symptoms may be idental with signs of acute miliary

dissemination or there may be cl evidence of activity in the primary fo but not infrequently the meningitis may the only manifestation of activity of disease

Prior to the use of streptomycin tub culous meningitis terminated fatally almost one hundred per cent of the case With the use of this antibiotic the mortalit rate has now been lowered to a point where about twenty to twenty five per cent of the patients survive (for a year or more) Early diagnosis and immediate treatment increase the survival rate to forty per cent while late diagnosis and delayed treatment decrease the survival rate to seven per cent

A definite diagnosis of tuberculous meningitis can be made only by recovering the organism from the cerebrospinal fluid The findings in the fluid are however characteristic and a presumptive diagnosis can be made when typical abnormalities are present These include An increased pressure a slightly cloudy or ground-glass appearance to the fluid with formation of a clot on standing a moderate pleocytosis varying between 25 and 500 cells per cu mm with lymphocytes as the predominating cell type increased protein content decreased sugar content with values in the range of 20–40 mg per 100 cc decreased chloride content negative Wassermann test and absence of growth when the fluid is inoculated on routine culture media

Treatment should be started without delay when there is definite or strong presumptive evidence of tuberculous meningitis It is not necessary to have bacteriologic confirmation before starting treatment Streptomycin *p*-aminosalicylic acid and promizole are the available therapeutic agents The optimum duration of treatment has not been definitely established as yet

Streptomycin should be given both intramuscularly and intrathecally when treating tuberculous meningitis

* also Chapter 18

sinuses the penicillin should be maintained for at least eight weeks

All the supportive measures indicated in the management of acutely ill patients may be necessary These include feeding by nasal tube adequate control of the fluid balance and blood transfusions The seizures which may be present in the acute stage and postoperatively should be treated with phenobarbital and/or diphenylhydantoin sodium The anticonvulsant medication should be maintained for an indefinite period

EPIDURAL ABSCESS

Infection of the epidural fat with resulting abscess formation may occur as the result of metastasis from staphylococcic infection of the skin or it may be secondary to osteomyelitis of the spine Unless the diagnosis is made early and treatment instituted immediately there is usually irreparable damage to the spinal cord or spread of the infection to the leptomeninges

The diagnosis of epidural abscess should be suspected when a patient with furunculosis or some other pyogenic infection due to staphylococcus rapidly develops symptoms and signs of cord compression These symptoms consist of radicular pain in the thoracic lumbar or cervical region rapidly progressing weakness of the legs and disturbance of bladder control Continued compression of the cord or involvement of the blood supply may result in a complete flaccid paraplegia A lumbar puncture usually will establish the diagnosis In the typical case pus will be aspirated before the subarachnoid space is punctured[1] or there will be complete or incomplete spinal subarachnoid block the cerebrospinal fluid will be cloudy and contain a moderate or large number of cells predominantly polymorphonuclear leukocytes the sugar content will be normal A very low sugar content or the presence of bacteria indicates that the infection has spread into the pia arachnoid

The patient should be treated in a hospital by a competent neurologic surgeon The treatment of choice is the use of chemotherapy combined with surgical drainage of the abscess Penicillin should be given intramuscularly in doses of 300 000 units every four hours before the operation and for a week or more postoperatively If laminectomy is performed and adequate drainage established before paraplegia has developed complete recovery can be expected If drainage is delayed until after paraplegia has developed the degree of recovery will depend chiefly upon the nature of the damage to the cord If the disturbance of cord function is the result of pressure only good results may be expected Poor results are usually due to necrosis of the cord secondary to thrombosis of its blood supply

[1] Puncture should be carefully performed with aspiration of the needle as the subarachnoid space is approached If pus is evacuated the needle should be withdrawn before puncturing the subarachnoid space

Virus Diseases

THE following infections of the nervous system are recognized as being of virus origin

Acute anterior poliomyelitis
Equine encephalitis—Eastern Western and Venezuelan types
St Louis encephalitis
Japanese B encephalitis
Lymphocytic choriomeningitis
Mumps meningoencephalitis
Herpes zoster (?)
Encephalitis lethargica (?)

to guide the neurosurgeon in regard to the optimum time for performing an operation for excision of a brain abscess Ideally the operation should be delayed until the infection has been completely circumscribed by a fibrous capsule This usually occurs within two to three weeks after the onset of the cerebral infection Unfortunately owever the age of the cerebral infection n not always be determined by the du ion of clinical symptoms As a rule how ever the diagnosis of a brain abscess is rarely established before the indicated time for operative intervention

When the diagnosis of a brain abscess is considered and it is not deemed advisable to operate penicillin should be adminis tered immediately in daily intramuscular doses of 600 000 to 1 200 000 units

When the site of the abscess can not be determined by clinical signs and symptoms he lesion must be localized by electro ncephalography or ventriculography Ideally the entire abscess should be ex cised without rupturing the capsule If this is not possible the pus should be evacuated and the cavity packed with pieces of gel foam that have soaked up 20 000 units of penicillin dissolved in 10 cc of normal saline The wound is closed without drain age

Penicillin should be continued post operatively for two weeks in the same dos age as before operation Smear and culture of the pus from the abscess cavity is made as soon as possible and once the organism is isolated its sensitivity to penicillin is determined It may be necessary to give streptomycin in place of penicillin because the organism may lack sensitivity to peni cillin The streptomycin is given intra muscularly in 0 5 Gm doses every six hours for two weeks

If seizures are present they should be treated with phenobarbital and/or di phenylhydantoin sodium Many neuro urgeons prescribe anticonvulsant drugs prophylactically after any operation

SUBDURAL EMPYEMA (ABSCESS, PURULENT PACHYMENINGITIS)

Infection of the subdural s occurs secondary to a pansinus cated by frontal osteomyelitis ar abscess It may follow mastoiditis be secondary to distant foci of The most common causative age streptococcus The clinical picture characteristic and consists of he various degrees of stupor, Jackson generalized seizures, focal cerebral toms (hemiplegia aphasia) and ev of increased intracranial pressure cerebrospinal fluid is under increased sure The cell count varies from 150 to per cu mm with polymorphonucl leukocytes predominating The prote tends to be elevated but the sugar is no mal No organisms are found on smear o culture

The use of antibiotics and sulfonamides in the treatment of paranasal sinus infec tions is the best prophylactic measure against the development of subdural empyema *

Patients with subdural empyema should be treated in a hospital by a competent neurologic surgeon Penicillin in doses of 300 000 units should be given intramuscu larly every three hours as soon as the diag nosis is suspected Surgical treatment consists of drainage through an enlarged burr hole in the lateral frontal region The postoperative therapy will depend upon the identification of the organism and a de termination of its in vitro sensitivity to penicillin In uncomplicated cases the pen icillin should be continued for at least three to four weeks In cases in which there are complications such as osteomyelitis of the skull or thrombosis of th

* See also Chapter 4

The whole pack is changed every four hours until there is a definite decrease of pain There is no need for the immediate application of splints or plaster in the stage of early paralysis A board placed at the foot of the bed will give the patient something to rest his feet against and help him to shift his position It will also help *prevent shortening of the tendo achillis* The paralyzed limbs should be maintained in a comfortable and suitable position and as soon as the pain has subsided passive movement should be started to prevent stiffness and contractures Light massage is advisable to improve the circulation and maintain the tone of the affected muscles

In cases with bladder paralysis catheterization may be indicated If necessary tidal drainage may be instituted until the return of function Constipation may be an annoying symptom particularly in patients with abdominal muscle paralysis and is treated by the use of enemas

In the spinal type of poliomyelitis paralysis of the diaphragm is the indication for the use of the respirator Trained personnel who thoroughly understand the mechanism of the respirator should be available at such times Undue restlessness or anxiety may be premonitory symptoms of cerebral anoxemia and an indication for the need of artificial respiration

B Convalescent Paralytic Stage In the convalescent stage, which usually begins about two weeks after the onset of the paralysis major attention must be paid to muscle re education An accurate estimate must be made of the involved muscles and the amount of weakness present in them In this stage physical treatment is the most important step and when possible should be carried out under the supervision of an orthopedist and skilled physiotherapist The important therapeutic steps consist of muscle re education the use of assistive supportive and protective apparatus and gait training Great care must be taken to prevent musculoskeletal deformities which result from the overuse of normal muscles unopposed by weakened or paralyzed muscles

C. Chronic Paralytic Stage In this stage orthopedic surgical treatment is carried out to correct or prevent deformities and to *increase functional capacity* The operations performed include tenotomies and muscle transplantations

To the lay person *infantile paralysis is a* terrifying disease It is desirable that the physician be reassuring understanding and encouraging at all times He must supply the encouragement that is necessary for the long, tedious months of muscle training and he must be able to help the family and the patient to adjust to the possible handicap that will result from permanent paralysis of some muscles

BULBAR POLIOMYELITIS

This form of poliomyelitis carries with it the highest mortality rate Careful and painstaking nursing care is essential Again treatment is entirely supportive and symptomatic Patients who are unable to swallow must have their nutrition and fluid balance maintained by nasal tube feedings or parenteral methods When there are accumulations of mucus in the pharynx the patient should be placed in a prone position with the foot of the bed elevated When available suction should be utilized When the respiratory center is involved and there is evidence of respiratory difficulties such as dyspnea periods of apnea increasing pulse rate or cyanosis oxygen should be supplied by mask or nasal tube Intubation or *tracheotomy may be necessary* in some of these cases

The respirator may be of value for some patients with bulbar poliomyelitis but it is used most effectively in cases with intercostal and diaphragmatic weakness

With the exception of acute anterior poliomyelitis and herpes zoster most of these virus produced diseases are relatively rare The general symptoms of involvement of the nervous system are essentially the same in all the types These symptoms may consist of evidence of meningeal irritation —headache and stiff neck and changes in the state of consciousness varying from drowsiness to coma The specific neurologic symptoms depend upon the part of the nervous system involved by the virus The cerebrospinal fluid may be under increased pressure and there is usually a pleocytosis with lymphocytes predominating The protein in the fluid is usually increased but the sugar and chlorides are normal The laboratory diagnosis of the viral diseases is difficult and only a few special laboratories have the facilities for such studies

There is no specific therapy for any of the virus infections of the nervous system The sulfonamides and the available antibiotics are of no value Treatment is therefore purely symptomatic and supportive The management of poliomyelitis and herpes zoster will be discussed in detail since they are the most common virus infections of the nervous system

ACUTE ANTERIOR POLIOMYELITIS

Prophylaxis

During an outbreak of poliomyelitis it is advisable to keep children from associating with large crowds such as would be present at parks beaches and theaters Elective tonsillectomy and adenoidectomy should not be done during poliomyelitis epidemics or during the months of August September and October Those in immediate contact with patients with poliomyelitis should not be allowed to work as foodhandlers for a period of at least two weeks after the onset of the illness

Nonparalytic and Preparalytic Stages

Many patients do not develop paralysis and it is therefore difficult to evaluate any type of treatment There is no statistical evidence to indicate that the use of serum or gamma globulin is of any value in preventing paralysis In the very early stages it is impossible to determine if paralysis will develop Therefore, all suspected cases of poliomyelitis should be confined to bed for at least four days after the temperature subsides Cases in which the diagnosis of nonparalytic poliomyelitis has been established should be kept in bed for ten days after the appearance of the first symptoms under close observation Only supportive measures such as the use of 0 3–0 6 Gm of aspirin for the headache and 0 03 Gm of phenobarbital for the restlessness are indicated at this time The muscle pains can be helped by the application of hot wet packs (see below) every three to four hours for several days

Paralytic Stage

A. Acute Paralytic Stage Such cases probably are managed best in a hospital although with good nursing care many patients can be treated at home The treatment is entirely symptomatic and consists of careful nursing the relief of muscular pain and limited physiotherapy

In the acute stage a light diet should be given and an adequate fluid balance maintained As the paralysis develops the patient may be apprehensive restless and in great pain Mild sedatives such as phenobarbital in doses of 0 03 Gm two to four times a day or 1 Gm of chloral hydrate two to three times may be of value in controlling the restlessness and apprehension When hyperesthesia of the extremities is present the handling and bathing of such patients should be minimal

Muscle pain is relieved by application of moist heat to the affected parts Pieces of flannel which have been soaked in hot water and wrung out are wrapped around the involved extremity and covered with oiled silk or cellophane to slow the cooling

Parasitic Diseases

PARASITIC infestation of the central nervous system is relatively rare in this country Involvement of the nervous system, when it does occur is usually secondary to visceral infection *

TRICHINOSIS

In the United States, *Trichinella spiralis* is the most common parasite which invades the nervous system Mental symptoms, signs of meningeal irritation, aphasia, hemiplegia and clinical syndromes resembling polyneuritis and acute anterior poliomyelitis are said to occur in about ten to seventeen per cent of all cases of trichinosis There is no specific therapy

CYSTICERCOSIS AND ECHINOCOCCOSIS

Certain parasites give rise to parasitic tumors in the brain The two most common are the larvae of *Taenia solium* (*Cysticercus cellulosae*) and *Taenia echinococcus* (hydatid worm) These larval forms may give rise to solitary or multiple cysts which may be in the meninges, the cortex, the deeper parts of the brain the ventricles and in the subtentorial regions The clinical manifestations are similar to those resulting from tumors in those areas When possible, the cysts should be evacuated by a competent neurologic surgeon In general, the surgical treatment of these tumors has not been entirely satisfactory

SCHISTOSOMIASIS

Kane and Most have recently reported a study of schistosomiasis of the central nervous system In schistosomiasis neurologic manifestations are due to the presence of the ova of *S mansoni*, *S haematobium*, or *S japonicum* within the brain or spinal cord In *S mansoni* and *S haematobium* the neurologic clinical manifestations are primarily of spinal cord origin, e g, transverse myelitis With *S japonicum* the neurologic manifestations are essentially of cortical, subcortical, or meningeal origin, such as monoplegias or hemiplegias encephalitis meningitis, and syndromes simulating brain tumor

The specific treatment for cerebral schistosomiasis (*S japonica*) is antimony potassium tartrate U.S P given intravenously in total doses of 2 22 Gm Although this compound does not alleviate the clinical manifestations that result from occlusion of cerebral vessels, it prevents further deposition of eggs in the brain by destroying the adult worms Kane and Most recommend the following treatment schedule

Eight cubic centimeters of a freshly prepared 0 5 per cent solution is given intravenously on the first day This is followed by doses of 12, 16, 20, 24 and 28 cc. on alternate days This last maximum single dose is repeated on alternate days until a total of 444 cc has been given The common complications that occur during treatment are cough immediately following an injection, arthralgia and electrocardiographic changes These rarely require interruption or discontinuance of therapy Neurosurgical intervention is indicated for the relief of symptoms of increased intracranial pressure or for the removal of a gross focus of infection

* See also Chapter 9

HERPES ZOSTER*

The causative agent of herpes zoster is thought to be a virus closely related to that of varicella In this condition there is usually a constitutional reaction with or without pain along the course of the affected root segment On about the fourth or fifth day crops of vesicles appear in the distribution of one or more posterior root ganglia The disease is self limited, lasting from one to three weeks The pain however may persist for months to years giving rise to the condition known as postherpetic neuralgia Ear pain vesicular eruptions in the external auditory canal and facial paralysis on the same side indicate involvement of the ganglion of the seventh nerve (Ramsay Hunt syndrome) Pain and a vesicular eruption in the distribution of the ophthalmic division of the fifth nerve are evidence of involvement of the gasserian ganglion In this form there may be ulcerations and opacities of the cornea on the affected side

While the therapy of herpes zoster has always been considered to be entirely symptomatic Finland and his co workers have suggested that aureomycin may be an effective agent in the treatment of this disorder In some cases aureomycin not only seemed to halt the progress of the disease but also brought about a rapid healing of the lesions In many cases the vesicles dried up and became encrusted in the first two to four days after treatment was started and proceeded to heal rapidly and completely thereafter In addition the pain accompanying the acute lesions might subside after the first day of therapy

Chloramphenicol has also been used in the treatment of herpes zoster but the results have been equivocal

Aureomycin Therapy Finland and group recommend that the aureomycin given in an oral dosage of 4 Gm daily Gm after each meal and at bedtime) two to four days or until the lesions are well dried and encrusted Half this dose Gm) should be given for an additional three to five days. This latter dosage may be used throughout if larger doses are not tolerated

Symptomatic Therapy There are a variety of medications that can be used locally for the skin eruption Boric or zinc oxide powder may be dusted on the lesions two or three times a day and covered by a dry dressing Collodion dressings may be used in place of the powder For ophthalmic herpes, the use of 2 per cent boric acid solution castor oil instillations atropine, and a protective pad are indicated

The pain in mild cases may respond to 0 3–0 9 Gm of aspirin three or four times a day The addition of codeine, 0 03 Gm, to the aspirin may be necessary in some cases Tetraethylammonium chloride has been recommended for the pain of herpes zoster It is given in doses of 50–250 mg intramuscularly or intravenously repeated daily if temporary benefit is obtained A dose every second or third day may be sufficient In some cases deep roentgen therapy will relieve the pain and shorten the course of the disease Two hundred roentgen units are directed to the region of the involved dorsal roots every other day for three treatments

Postherpetic neuralgia is a poorly understood and difficult condition to treat Section of the affected posterior roots has not been too successful in bringing about relief of pain Roentgen ray irradiation of the spinal cord and nerve roots or of the Gasserian ganglion may be effective in some cases

* See also Chapters 4 and 58

vasodilators the anticoagulants, and the vitamins, particularly thiamine hydrochloride have been tried None of these has proved to be of definite value but may be beneficial for their psychotherapeutic and tonic effects Arsenic may be given in the form of one of the arsphenamines intravenously at weekly intervals for a period of four to six weeks or it may be given orally as Fowler s solution, beginning with one drop three times daily, increasing up to 10 drops three times a day for a period of six weeks A rest period of the same length of time should intervene before the next course Quinine is usually given as the hydrochloride in a dose of 0 3 Gm once or twice a day for several weeks The anticoagulants dicumarol and heparin, have not produced convincing results and in addition may produce massive hemorrhages

Physiotherapy

Massage and passive movement of the weakened spastic limbs is of some value Muscle training is of value from both a physical and psychologic point of view

Psychotherapy

Encouragement and reassurance are essential Invalidism should be avoided as long as possible and the hopeless outlook should be minimized It is probably best to maintain some form of therapy constantly

Fever Therapy

This form of treatment has caused acute exacerbation of the disease and is not recommended

DIFFUSE SCLEROSIS (SCHILDERS DISEASE)

This condition is similar to multiple sclerosis but is more rapidly advancing and widespread Patients may develop blindness, deafness aphasia and paralysis The treatment is the same as for multiple sclerosis

ACUTE ENCEPHALOMYELITIS

This condition is characterized by an acute and widespread involvement of the central nervous system It is thought by some that it attacks the nervous system only once and results either in death or in a complete or partial recovery The spinal fluid frequently contains cells and protein values over 100 mg per 100 cc are not infrequent The treatment is the same as for the postinfectious and postvaccinal encephalomyelitides

Diseases of the Nerves

MONONEURITIS

Dysfunction of the individual peripheral nerves frequently results from compression or tearing In these cases the purpose of treatment is to maintain the nutrition of the paralyzed muscles prevent contractures, and keep the joints mobile These treatment measures are best carried out by a skillful physiotherapist * If there is a possibility that the loss of nerve function is the result of a tear or of constriction by scar tissue consultation should be held with a neurologist and/or neurosurgeon as to the advisability of surgical treatment

SCIATICA (SCIATIC NEURITIS)

Pain in the distribution of the sciatic nerve may be caused by perineuritis of the sciatic nerve or may be secondary to com

* See also Chapter 45

Postinfectious and Postvaccinal Encephalomyelitides

MEASLES German measles scarlet fever, chickenpox, smallpox, vaccination against smallpox or rabies, and mumps may be complicated by an acute disseminated encephalomyelitis The symptoms usually develop between the fifth and fifteenth day after the onset of the original disease or the first inoculation In measles and scarlet fever the encephalitis may develop while the rash is still present There may be evidence of involvement of the cerebrum or spinal cord with convulsions hemiplegia, or transverse myelitis

There is no specific therapy treatment is symptomatic and supportive Patients should be kept in bed during the period of acute illness Fluid balance and nutritional needs should be maintained parenterally and by stomach tube if necessary For adults an adequate fluid intake is 3000 cc, for children it is correspondingly less

Many patients are very restless and sedation may be necessary In such cases sodium phenobarbital 0 12 Gm intramuscularly every four hours is usually an effective sedative Paraldehyde can be given orally in doses of 8 to 15 cc or by rectum in doses of 15 to 30 cc In children, chloral hydrate 0 3 Gm by rectum is frequently effective

Constipation and abdominal discomfort and distension may be annoying symptoms In such cases enemas are indicated as necessary For the few patients who require catheterization, 0 5 Gm sulfadiazine should be given three times daily as a prophylactic measure against the development of urinary tract infection

Demyelinizing Diseases

MULTIPLE SCLEROSIS

Multiple sclerosis is one of the more common neurologic diseases The dissemination of the lesions in time and space is pathognomonic At any one time there is usually evidence of multiple lesions, and from time to time there is a change in the number or character of the lesions The spinal fluid is normal in over half the cases The most characteristic abnormality is a first zone (paretic) gold curve

There is no specific therapy It is difficult to evaluate the effect of any type of treatment because of the frequent spontaneous remissions in this disease

General Care of the Patient

As a rule there is no need to confine the patient to bed and every effort should be made to keep the patient as near a normal level of activity as is consistent with his physical state Overwork and fatigue, however should be avoided Bedridden patients should be carefully observed for the development of bedsores and efforts should be made to prevent urinary tract infections The use of 10 drops of tincture of belladonna three times a day, may be helpful in controlling urinary frequency A bag may be worn over the penis for incontinence When diplopia is present a patch should be worn over one eye

Use of Drugs

Pharmacologic measures have been used for many years in the treatment of multiple sclerosis and new drugs are constantly being tried Arsenic and quinine are some of the older drugs still in use, and more recently prostigmin histamine, cytochrome C, the

be applied to the forearm and hand in such a position as to maintain the hand in slight extension and the fingers in slight flexion

Physiotherapy should be started as soon as excessive tenderness of the muscles has disappeared * Gentle massage of the muscles should be carried out daily Passive movements of the joints should be started at the same time as the massage in order to keep the joints freely movable and to prevent development of arthritic changes or contractures The patient should be encouraged to carry out active movements to a degree consistent with comfort and his physical state In the more chronic stages muscle training may be necessary

The relief of pain is an essential step in the treatment of polyneuritis The analgesics should be used freely Acetylsalicylic acid 0 3–0 6 Gm can be given every two to three hours as required At times it may be necessary to add 60 mg of codeine to the acetylsalicylic acid When a patient is not benefited by this combination some relief of pain may be obtained by the use of 50 mg demerol three to four times a day Even more helpful than the use of drugs is the application of hot wet packs to the affected extremities leaving the joints uncovered so that passive movement can be carried out

Vitamins particularly thiamine hydrochloride have been given in massive doses They are undoubtedly of value for patients with obvious vitamin deficiency, but it is highly doubtful whether vitamins in excess of those contained in a well balanced diet will have any effect on recovery

More recently BAL has been recommended for the severe forms of polyneuritis irrespective of its cause The rationale for its use is the fact that this compound removes heavy metals and toxins from the enzyme systems that regulate carbohydrate and fat metabolism and which may be disturbed in polyneuritis BAL is given intramuscularly in doses of 1 5–3 mg /kg of body weight daily This dosage should be continued for approximately two weeks However, the drug is not free of harmful side effects and caution must be exercised in its use In our experience benefit from its use has been doubtful

* See also Chapter 45

In one of the more common types of polyneuritis infectious polyneuritis there may be paralysis of the intercostal muscles and the diaphragm In such cases the patient must be placed in a respirator and kept there until these muscles recover

NEURALGIAS

Trigeminal Neuralgia (Tic Douloureux)

This syndrome occurs in middle-aged or elderly individuals and is characterized by paroxysmal attacks of sharp stabbing pain in the distribution of one or more branches of the fifth cranial nerve

The best treatment is either surgical section of the trigeminal root or division of the descending root of the fifth nerve in the medulla When surgery is not performed patients can obtain relief from the paroxysms for a period of six to twelve months by an alcohol injection of the affected branch When successful this results in complete anesthesia in the distribution of the injected branch

There is no adequate medical treatment The vitamins are of doubtful value During paroxysms in mild cases 15 to 20 drops of *trichloroethylene* sprinkled on gauze or a handkerchief can be inhaled and may give temporary relief The drug must be taken lying down as vertigo and drowsiness may be side effects

Glossopharyngeal Neuralgia

This is a rare type of neuralgia characterized by recurrent attacks of severe pain in the back of the throat tonsils back of the tongue and middle ear

The treatment of choice is the intra

pression of the nerve by a tumor mass in the pelvis arthritic changes in the sacroiliac joint or pressure on the nerve roots within the spinal canal exerted by a tumor or ruptured intervertebral disc The latter is probably the most common cause

The clinical manifestations of sciatica are pain and paresthesias along the course of the nerve starting usually in the sciatic notch with radiation down the posterior surface of the thigh and leg to the plantar surface of the foot On examination there is limitation of straight leg raising diminution or absence of the ankle jerk and perhaps tenderness to pressure over the sciatic notch and in the distribution of the sciatic nerve

Every effort should be made to determine the cause of the sciatic pain and when possible the causative agent should be removed

Conservative Treatment

This form of therapy should be utilized when no obvious pathologic condition is found and during the first attack of pain due to a ruptured intervertebral disc The patient should be kept flat in bed on a hard mattress or on one which has boards under it for a period of three to four weeks Heat may be applied externally by the use of an electric bulb in a cradle over the patient s legs When there is root compression by a disc daily shortwave diathermy in combination with infra red irradiation twice a day applied to the lumbar area may be of value

Analgesics are usually necessary for the relief of pain Acetylsalicylic acid 0 6 Gm every two to three hours may give some relief If this is not effective it may be necessary to give 50 mg of demerol three to four times a day by mouth Morphine should be avoided Curare and mephenesin (tolserol) by parenteral injection have been effective in some cases in relieving the spasm of the paravertebral muscles which accompanies a ruptured intervertebral disc

A well fitting corset or brace may be helpful when the patient becomes ambulatory

Surgical Treatment

When there is x ray evidence of pathologic change in the sacroiliac joint fusion of the joint may be effective in relieving the pain in some cases

A ruptured intervertebral disc usually can be demonstrated by the intraspinal injection of an opaque medium such as pantopaque This procedure should be carried out by a neurologist or a neurosurgeon The present tendency is to treat the initial attack of pain conservatively If there are repeated attacks of pain the disc should be removed surgically by a competent neurosurgeon

POLYNEURITIS (MULTIPLE PERIPHERAL NEURITIS)

A great number of poisons and metabolic disturbances can produce polyneuritis Although there may be some variation in the distribution of the paralyses and in the degree of associated sensory loss the clinical picture is similar regardless of the cause

Whenever possible the causative agent should be removed or the appropriate treatment instituted Bed rest is essential during the acute stage because the heart muscle may be involved The patient usually can be allowed up when the pulse rate has returned to normal and strength has returned to the affected muscles An adequate dietary and fluid intake is important

A cradle should be used to keep the weight of the bedclothes from the lower limbs and the patient can be made more comfortable by the use of pillows beneath the knees A board or a rolled blanket should be placed at the foot of the bed to counteract the footdrop To prevent the stretching of the extensor tendons of the wrist that result from the wrist-drop cock up splints well padded with cotton should

fate Objective and subjective improvement in muscular power is recorded at intervals from ten minutes to eight hours Improvement should be marked after twenty to thirty minutes and be maintained for a period of two hours There is a gradual decline to the previously easily fatigable state in a period of four to eight hours

In the mild and moderate cases neostigmine is given orally in the form of neostigmine bromide The dosage schedule should be arranged to cover periods of expected muscle weakness and to permit increased activity Usually 1–2 tablets (15–30 mg) are given every three to four hours Some patients may require as many as 30 tablets a day

In severe cases it may be necessary to give 0 25–0 5 mg of neostigmine intramuscularly three times a day in addition to the oral neostigmine The parenteral dose is probably best given thirty to sixty minutes before a meal or as necessary to control the marked weakness

Side Effects of Neostigmine These are primarily gastrointestinal disturbances and consist of anorexia nausea vomiting abdominal distress and diarrhea When these untoward effects are present they can be fairly readily controlled by the administration of atropine in the form of tincture of belladonna 10 drops three times a day or as atropine sulfate 0 4 to 0 6 mg three times a day The abdominal discomfort may be relieved, in some cases by the eating of a cracker piece of toast or the drinking of some milk

Adjuvant Drugs *Ephedrine sulfate* 0 025 Gm four to six times a day is useful for some patients as adjuvant therapy with neostigmine It is best not to give this drug after 4 00 P M as it may interfere with sleep

Potassium chloride 1 Gm three to six times a day occasionally has been beneficial in supplementing the effect of neostigmine Guanidine hydrochloride has also been found effective in relieving the myasthenic symptoms in some patients It can be used alone or in conjunction with neostigmine in a dose of 0 13 Gm three to six times a day

New Drugs Recently a new compound tetraethyl pyrophosphate (TEPP) has been introduced for the treatment of myasthenia gravis Ten milligrams of TEPP given orally is said to be as effective as 100–150 mg of neostigmine In addition its duration of action is from twenty four to forty eight hours in contrast with the two to three hours of neostigmine The outstanding objection to TEPP at the present time is the fact that there is an exceedingly narrow range between the dose that produces maximal response and the dose that causes toxic symptoms

Surgical Treatment *Thymectomy* There has been considerable difference of opinion regarding the value of thymectomy in the treatment of myasthenia gravis One recent study has indicated that the operation is only of value in certain types of cases Eaton and Clagett concluded from a comparison of 72 cases in which surgical treatment was employed with 142 control cases in which nonsurgical treatment was used that thymectomy did not beneficially influence the course of myasthenia gravis They believe that a thymectomy is indicated only when the following criteria are present (1) A thymic tumor can be demonstrated roentgenologically (2) The condition of the patient is such that the risk of operation is not considered excessive (3) There is no roentgenologic or clinical evidence of inoperability of the tumor

General Information for the Patient Patients should be advised that respiratory infections may lead to a marked increase in their symptoms All patients with myasthenia gravis should carry ampules of neostigmine methylsulfate a hypodermic syringe, and a note describing their condition and directions as to what should be done in an emergency

cranial section of the glossopharyngeal nerve Occasionally the paroxysms may be lessened by cocainization of the tonsils and pharynx

Meralgia Paresthetica

In this condition there are paresthesias in the anterolateral surface of the thigh These are probably caused by constriction of the lateral femoral cutaneous nerve at the point where it pierces the fascia about 4 inches below Poupart's ligame The symptoms are often self limited a may disappear without any treatment T use of constricting belts and corsets shoul be prohibited Local infiltration with pr caine of the paresthetic area may affor immediate relief If this treatment is not successful the fascia lata can be divided at the point of emergence of the nerve

Degenerative Diseases

DEGENERATIVE DISORDERS OF THE NEUROMUSCULAR APPARATUS

The diseases that come under this heading are those in which the symptoms are caused by weakness of the somatic musculature They consist of the muscular dystrophies myasthenia gravis and familial periodic paralysis

Muscular Dystrophies

There is no specific treatment for the muscular dystrophies Massage may delay the development of contractures Every ef fort should be made to keep the patient active and leading as normal a life as possible The vitamins particularly vitamin E have been tried in large doses without ny beneficial effect The myotonia in yotonia dystrophica can be relieved by the ily use of 0 6–2 Gm of quinine hydrolorıde

asthenia Gravis

yasthenia gravis is characterized by ormal fatigability and weakness of the cles While any of the muscles of the may be affected the bulbar muscula (eye facial palatal and pharyngeal) st frequently involved In this disease is probably a deficiency in the formation of acetylcholine or an excess of its antagonist the esterases Action of the esterases is inhibited by physostigmine compounds and allows the action of the acetylcholine to be prolonged

General Management Patients should be advised to restrict their activities to a level consistent with their physical state Overwork and excessive fatigue should be avoided Complete rest is essential during exacerbations As a rule the patient may have a general diet but in severe cases however a soft or liquid diet should be given and it may be necessary to resort to tube feedings Severe respiratory embarrassment is an indication for the use of a respirator Careful nursing is essential at such times Suction and postural drainage are helpful in removing the accumulation of secretions in the pharynx that may cause obstruction of the airway Bronchial mucus plugs should be removed by bronchoscopy

Pharmacotherapy *Neostigmine* At the present time neostigmine is the most effective drug To determine the effect to be expected from neostigmine first the relative strength of the various muscle groups is determined. The patient then is given subcutaneously the contents of a diagnostic ampule containing 1 5 mg of neostigmine methylsulfate and 0 6 mg of

mm At this level most patients will improve and further advance of symptoms will not occur

Folic acid (pteroylglutamic acid) is not recommended in the treatment of posterolateral sclerosis Neurologic complications of pernicious anemia have developed and progressed in some patients on folic acid even though their blood counts were within the normal range

More recently vitamin B_{12} a crystalline compound containing cobalt phosphorus and nitrogen has been used successfully in the treatment of pernicious anemia and its neurologic complications While the exact dosage of vitamin B_{12} cyanocobalamin has not been definitely established the amount used should be in excess of that needed by patients who have pernicious anemia without involvement of the nervous system Vitamin B_{12} is not effective when given by mouth and is best administered parenterally Fifteen micrograms should be injected intramuscularly daily or every other day for three to six months After this period maintenance doses of 15–30 μg should be employed at weekly intervals

DEGENERATIVE DISEASES OF THE CEREBELLUM (HEREDITARY CEREBELLAR ATAXIAS)

These are a group of closely related disorders that are usually hereditary or familial Other parts of the nervous system are involved in addition to the cerebellum There is a great variation in the different syndromes In addition to Freidreich s ataxia which is the most common the disorders in this group are hereditary spastic paraplegia Sanger Brown s ataxia Marie s cerebellar ataxia the various forms of progressive cerebellar degeneration and the Levy Roussy syndrome

There is no treatment which affects the course of the degeneration The patient should be encouraged to live as normal a life as possible Physiotherapy in particular muscle training may keep the spasticity and ataxia under some control

DISEASES OF THE BASAL GANGLIA

Under this heading the following syndromes are considered Parkinsonism Huntington s chorea progressive hepatolenticular degeneration (Wilson s disease) torsion dystonia (dystonia musculorum deformans) and spasmodic torticollis

All these conditions are characterized by disturbances in muscle tone and by the presence of abnormal movements With the exception of parkinsonism treatment of these disorders has been unsatisfactory

Parkinsonism

This syndrome is the result of diffuse damage to the basal ganglia produced by infections toxic agents arteriosclerosis or senile changes Clinically there is slowness of movement weakness muscular rigidity and tremor Other symptoms that may be present include excessive salivation impaired eye movements particularly convergence oily skin nocturnal incontinence pains in the extremities respiratory tics and spasmodic contractions of the eye muscles (oculogyric crises)

The treatment of parkinsonism is entirely symptomatic Complete relief from the symptoms is rarely possible but a moderate degree of improvement can be obtained in all patients Results of treatment are best in patients with a predominance of spasticity and little or no tremor With treatment these patients note a lessening of their rigidity and are able to perform their routine tasks more easily The salivation pain in the extremities and the retropulsion usually are amenable to therapy but the tremor is often quite resistant Oculogyric crises which respond poorly to the belladonna alkaloids alone may be relieved by combining them with amphetamine sulfate This latter drug is valuable as an adjuvant to combat the excessive drow



Family Periodic Paralysis

This is a rare condition in which there are periodic transient attacks of paralysis of the muscles of the trunk and extremities without loss of consciousness During an attack the reflexes are absent and the muscles cannot be stimulated electrically The duration of an attack varies from a few to twenty four hours or more and the frequency varies from many attacks a month to one or two a year The disease is familial and the attacks of paralysis are related to a sudden drop of the potassium content of the serum The weakness disappears when the serum potassium returns to normal levels Attacks may be precipitated by high carbohydrate intake exposure to cold excessive drinking constipation overexertion fatigue and emotional upsets

The precipitating factors should of course be avoided Since the cause of the disturbed potassium metabolism is unknown treatment is directed toward restoring the potassium level of the serum to normal Immediately upon the onset of an attack potassium chloride should be given by mouth in doses of 5-15 Gm This can be given in a 25 per cent aqueous solution 2 Gm (8 cc) every hour until the patient has recovered In extremely severe attacks with weakness of the muscles of respiration and deglutition artificial respiration should be applied and potassium chloride administered intravenously in doses of 50 cc of a 2 per cent solution

To prevent the occurrence of attacks potassium chloride should be taken daily The amount required varies with each patient and must be determined by trial As a rule from 4 to 8 cc of a 25 per cent solution of potassium chloride is administered two to four times daily

DEGENERATIVE DISEASES OF THE SPINAL CORD

Amyotrophic lateral sclerosis syringomyelia and posterolateral sclerosis are the more common degenerative disorders spinal cord

Amyotrophic Lateral Sclerosis

There is no specific treatment and drug or vitamin has proved to be of va Physiotherapy will maintain the nutri of the wasted muscles and relieve spasticity for as long as possible W there is difficulty in swallowing a soft d should be recommended and in advance cases it may be necessary to resort to tub feedings

Syringomyelia

Treatment is entirely symptomatic and supportive Appropriate orthopedic appliances should be used to protect the hands feet and joints when trophic disturbances are present In occasional cases with complete subarachnoid block drainage of the syringomyelic cavity after laminectomy may be of some benefit

Roentgen irradiation while not always successful is the best treatment at present Diffuse treatment should be given over the entire spinal cord with concentration over the affected sites

Posterolateral Sclerosis (Combined System Disease)

This is a degenerative disease of the spinal cord that is usually associated with primary anemia * although it may occur with secondary anemia pellagra and in severe nutritional deficiences without anemia Early manifestations are paresthesias in the toes and fingers Other symptoms are weakness of the legs ataxia and disturbances in bladder control

The treatment in posterolateral sclerosis is usually the treatment for pernicious anemia Liver extract 15 units U S P in 1 cc is given intramuscularly one or more times a week The red blood cell count should be maintained at 5 000 000 per cu

* See also Chapter 14

instilling one or two drops of 0 5 to 1 per cent aqueous solution of eserine into the eye *The prolonged use of eserine can produce conjunctivitis* it may be advisable to prescribe eye glasses with a 1 or 2 diopter + lens for reading Pilocarpine 0 006 Gm may be given by hypodermic injection to counteract the side-effects of belladonna

New Drugs

More recently a variety of new drugs have been given a clinical trial for the treatment of parkinsonism The new compounds include mephenesin (tolserol) parpanit, artane diparcol dihydro *beta-erythrodione and diphenhydramine* (benadryl) It is too early to evaluate the actual efficacy of these new drugs In general in the treatment of parkinsonism, it appears that these new compounds are not superior to the solanaceous drugs except that some produce less undesirable side reactions than do the belladonna group When they are of therapeutic value the rigidity is improved They are reported to be more effective when used in combination with the alkaloids of the belladonna root than when used alone

Two of these compounds artane and diphenhydramine, are being used more extensively than any of the other new drugs

Artane is a synthetic antispasmodic compound The average dose is 8 mg a day *Treatment* is best started by giving an initial dose of 1 mg four times a day, before meals and at bedtime When it becomes evident after several days that the *patient is not sensitive* to the drug and is not experiencing disagreeable side reactions the dose is increased gradually by 1 mg per day to 2 mg four times a day Some *patients are unable to* tolerate more than 3–4 mg a day while others can easily take *up to 20 mg a day*

The side effects most frequently noted *with this compound* are dryness of the mouth nausea giddiness blurring of vision, nervousness, tinnitus, and soreness of the mouth

Diphenhydramine is usually given in 50 mg doses three or four times a day in conjunction with some one or combination of other drugs The somnolence that occurs in a certain number of patients as the result of the use of diphenhydramine can be fairly readily counteracted by the use of amphetamine

Psychotherapy Drug therapy alone is not enough and without some form of psychotherapy the treatment of Parkinsonism is rarely successful Many consider psychotherapy to be the factor responsible for the therapeutic success attributed to some new drug or to a change in medication The administration of a new drug is combined as a rule, with repeated examinations and a great deal of individual attention to the patient Elaborate questioning and examination commendable as they are, carry with them a certain amount of suggestion and become simple psychotherapeutic procedures

The psychotherapy need not be elaborate or technical but should consist for the most part of explanation reassurance encouragement and sustained interest on the part of the physician Many patients with Parkinsonism are convinced that their condition is hopeless and believe that they will rapidly become physically and mentally incapacitated They are usually embarrassed by their appearance and are fearful that their economic security will be threatened by their disability Emotional disturbances of any kind tend to accentuate the symptoms of Parkinsonism and make the condition worse

A great deal can be accomplished psychotherapeutically if the patient is seen fairly frequently and is made to understand that the disease is only slowly progressive and is never accompanied by intellectual deterioration Patients should be encouraged to continue at their work as long as possible

siness or the mental depression which is common in these patients

The alkaloids of belladonna root singly or in combination have proved to be the most satisfactory mode of therapy The actual preparation that is used is of slight importance compared to the regulation of the dosage Treatment should be started with a very small amount of the alkaloid and gradually increased over a period of weeks until the development of untoward symptoms makes further increases inadvisable The optimum dose is usually slightly below this level

The following alkaloids of belladonna are the ones most commonly used

Hyoscine or *scopolamine* is usually given in the form of the hydrobromide starting with a daily dose of 0 33 mg and increasing after three to five days to 0 33 mg twice daily and after an equal interval of time 0 33 mg three times a day Further increases should be made by increments of 0 33 mg until the optimum dose is obtained

Stramonium which contains a mixture of atropine and hyoscyamine can be given as the tincture or in the form of pills At the beginning of treatment one 0 16 Gm pill is given daily increasing after three to five days to two pills daily with further increases by increments of 0 16 Gm until the optimum dose is reached Many patients can tolerate 0 66–1 0 Gm daily divided into four or five doses

Tincture of belladonna can be given but it usually produces untoward symptoms before the optimum therapeutic dose is reached

Favorable results have recently been attributed to Bulgarian belladonna The favorable results probably are due to the care which is taken in regulating the dosage and to the fact that a combination of alkaloids is more effective in nontoxic doses than any single one of its various alkaloids The two preparations which contain a mixture of the bell loids are vinobel and rabellon is a desiccated white wine extra belladonna marketed in tablets 0 4 mg and 0 8 mg of total alk method of administration is to be one tablet of 0 4 mg and gradual crease the dose at intervals of three days until the maximum therapeuti is obtained or until further incre dosage is contraindicated by the ap ance of toxic symptoms As a rule 3 mg of vinobel in a period of twenty hours can be tolerated

Rabellon is a synthetic compound c taining the various alkaloids in the sa proportion as they occur in the Bulgari root Each tablet contains 0 5 mg and scored to facilitate division The method of administration is the same as that for vinobel The usual range tolerated is one to three tablets three or four times daily

Amphetamine sulfate (benzedrine sulfate) can be given in conjunction with any of the belladonna alkaloids It is indicated when there is a complaint of somnolence or depression or when oculogyric crises are present The usual dose is 10 to 20 mg once or twice each morning

Toxic Effects of the Belladonna Drugs The effects of overdosage are dryness of the mouth pupillary dilatation and impairment of the ability to converge urinary retention dysphagia drowsiness nausea vomiting abdominal cramps diarrhea diplopia headache and mental confusion. Many of these symptoms can be avoided by starting with small doses spaced at intervals throughout the twenty four hours and increasing the dose slowly In some cases it is advisable to continue with a dose that produces mild reactions such as dryness of the mouth and difficulty in focusing the eyes Taking the medication after meals sucking hard candy or chewing gum may combat the dryness of the mouth T culty in convergence m

21. Diseases of the Nervous System

II. Functional, Traumatic, and Neoplastic Diseases

SIDNEY CARTER
& H. HOUSTON MERRITT

Paroxysmal Diseases

EPILEPSIES

Epilepsy is a symptom complex characterized by recurrent attacks of a sudden and transient disturbance of consciousness, with or without convulsive movements. The present tendency is to divide the disease into two groups, idiopathic and symptomatic epilepsy. A patient is said to have idiopathic epilepsy when no organic lesion of the brain or physiologic disturbance can be demonstrated as the cause of the seizures. About seventy-five per cent of the cases of epilepsy are of this type. Patients with symptomatic epilepsy are those in whom an organic lesion can be demonstrated in the brain or in whom there is some physiologic disturbance which is the underlying basis for the seizures.

Epileptic attacks can be divided into three types. Some patients may have only one type of seizure, but it is common for the afflicted individual to suffer with two or even three types of spells. The three types of attacks are: grand mal (including Jacksonian), petit mal, and psychic equivalent or psychomotor attacks. During a seizure there are disturbances in the electrical activity of the cortex which are characteristic of each of the three types of seizures. In addition, a vast majority of the patients with seizures show a paroxysmal abnormality of the electroencephalogram in the interval between attacks. It is to be remembered, however, that fifteen per cent of the patients with epilepsy will have a normal record when a tracing is taken in the seizure-free interval, so that the finding of an entirely normal electroencephalogram does not exclude the diagnosis of epilepsy.

There are three important steps in the treatment of epilepsy. The removal of

and to maintain social and recreational interests Every effort should be made to guide them through particularly trying emotional situations

Physiotherapy Patients with Parkinsonism tend to develop increasing rigidity flexion deformity contractures and pain For this reason physiotherapy is an essential part of the treatment of the disease To be of value it should be carried out daily The services of a skilled therapist are desirable but not essential Most patients and their families can be taught to carry out the necessary procedures which consist primarily of massage and active and passive movements at all joints of the involved extremities *

Surgical Treatment of Parkinsonism and Other Diseases of the Basal Ganglia

A variety of surgical procedures have been devised to relieve muscular rigidity spasticity and abnormal movements However there is no statistical evidence which indicates that any of the operations is entirely successful Surgical intervention is not to be recommended as a therapeutic procedure

The treatment used in parkinsonism can be tried in the other diseases of the basal ganglia but usually it is not satisfactory Compounds such as curare and mephenesin (tolserol) have been tried but the improvement that has resulted from intramuscular and intravenous injections of these drugs has been unsustained

* See also Chapter 45

PROGRESSIVE HEPATOLENTICULAR DEGENERATION

It has been suggested that a disturbance in copper metabolism may be one of the etiologic factors in hepatolenticular degeneration (Wilson's disease) The administration of BAL to patients with this disease has led to an increase in the excretion of copper As a result of these observations BAL has been given a therapeutic trial in hepatolenticular degeneration It has only been used in a small number of cases and while some favorable results have been reported it is too early to evaluate this form of treatment

DEGENERATIVE DISEASES OF THE CORTEX

Alzheimer's disease and Pick's disease the presenile dementias are the two most common conditions in this group Both diseases present essentially similar clinical pictures The gradual development in middle aged individuals of progressive dementia speech disturbances and occasionally convulsive seizures As a rule the two diseases can be differentiated only at the time of autopsy

There is no known treatment that influences the slow progressive course of the disease The progressive deterioration may make it necessary to institutionalize some patients Anticonvulsive medication as in the treatment of epilepsy is indicated when seizures are present *

* See also Chapter 2

must be determined by trial and error for each patient

Indications for Use of Specific Drugs In those patients who have infrequent grand mal seizures (one to four per year) *phenobarbital can be tried first because of* its high therapeutic index and its relatively low toxicity When the seizures are more frequent diphenylhydantoin sodium is the drug of choice A combination of pheno barbital and diphenylhydantoin sodium often is more effective than either of the drugs used alone when combined, a full therapeutic dose of each drug must be given Diphenylhydantoin sodium also is the drug of choice for patients with psycho-motor seizures Tridione is used in the treatment of patients with frequent petit mal attacks

Phenobarbital is distributed both in tablet and elixir form The tablets are available in three sizes 15 mg, 30 mg, and 100 mg The elixir contains 15 mg in each 4 cc For the average adult the initial dose of phenobarbital is 0 1 Gm daily given usually at bedtime If necessary this dose is increased gradually at two-week intervals until the patient is taking as much as 0 3 *to 0 4 Gm per day* If this amount is inef fective in controlling seizures it is doubtful whether further increase will be of value The dose of phenobarbital for children should be in proportion to their weight It has been found however that children are able to tolerate and require almost as large a dose as adults It is advisable therefore to give children over 6 or 7 years of age the minimum dose of 0 1 Gm per day

Toxic effects are rarely serious In about 5 to 10 per cent of patients, phenobarbital causes an incapacitating drowsiness In some patients, this will disappear with con tinued therapy in others the persistence of drowsiness may prevent further use of the drug Occasionally this drowsiness can be combated by the administration of 10-20 mg of amphetamine sulfate, in sin gle or divided doses given in the forenoon Less than 1 per cent of patients who re ceive the drug develop an allergic derma titis of a scarlatiniform or morbilliform nature In such cases the drug should be *temporarily withdrawn* until the rash dis *appears If the rash recurs on subsequent* administration, further use is contraindi cated because of the danger of exfoliative dermatitis Ataxia of the gait tremors of the extremities, and nystagmus can develop in almost all patients if large doses of phe nobarbital are given These symptoms are rare, however, with doses of less than 0 2-0 3 Gm *per day*

Diphenylhydantoin Sodium (dilantin sodium') is sold in capsules of two sizes 0 1 Gm (capsules with a circular red band) and 30 mg (capsules with a circular pink band) It is particularly valuable in grand mal and psychomotor attacks One of its notable advantages in addition to its effi cacy in controlling seizures is its lack of hypnotic activity The principle of admin istration of phenytoin sodium is similar to that of phenobarbital to establish and maintain a reservoir of the drug sufficient to control the seizures The minimum daily dose for the average adult is 0 3 Gm daily This can be given as a single dose at bed time or in divided doses during the day If this dose is not effective in controlling seizures, it can be gradually increased by 0 1 Gm every two weeks *until the seizures* are controlled or undesirable side-effects appear The maximum dose is 0 6 Gm daily, but very few patients can tolerate this amount For the majority of patients the optimum dose is 0 4 Gm daily *For* children over twelve or fourteen years old the average dose is 0 3-0 4 Gm and in younger children 0 2-0 3 Gm

This drug can produce *toxic effects* in the form of nervousness and sleeplessness gastric distress nausea and vomiting un steadiness of gait, hypertrophy of the gums dermatitis and psychotic symptoms The

etiologic and precipitating factors physical and mental hygiene and the use of anti convulsant medication

Removal of Etiologic and Precipitating Factors

All physical defects and abnormalities should be corrected if possible This would include the treatment of infections such as the meningitides and syphilis by appropriate chemotherapy and antibiotics Endocrine abnormalities such as hyperinsulinism should be treated surgically hypoparathyroidism by appropriate replacement therapy Operable tumors and abscesses of the brain should be removed surgically The advisability of removing cortical scars secondary to trauma vascular disease or birth injuries will be discussed under the surgical therapy of epilepsy

Physical and Mental Hygiene

The patient should be encouraged to live as normal and regular a life as possible While there are no particular dietary restrictions the epileptic patient should have a wholesome well balanced diet containing an abundance of fresh fruit and vegetables Alcoholic beverages of any kind are forbidden Constipation is frequently a troublesome symptom and can be controlled to a great extent by the judicious use of mild laxatives Patients should keep regular hours of sleep and have a set time for retiring and arising Dawdling in bed after the other members of the household have arisen should be discouraged A moderate amount of regular physical activity is desirable and even more dangerous sports such as swimming and horseback riding may be permitted when there are proper safeguards Epileptic patients should not be allowed to drive automobiles

Simple psychotherapy will help overcome feelings of inferiority and self-consciousness resulting from the attacks Education of the other members of the family in regard to their attitude toward the patient's illness is of great importance Excessive attention and oversolicitousness should be discouraged and the family should not be allowed to make a chronic invalid of the patient Efforts should be made to keep children in school and adults should be encouraged to work The aid of vocational rehabilitation centers should be obtained for specialized training and job placement if possible Commitment to an institution is not advisable unless mental deterioration or unduly violent or frequent attacks which can not be controlled by treatment, make it necessary

The Use of Anticonvulsant Medication

The elimination of causative and precipitating factors and the control of physical and mental hygiene are important steps in the treatment of epilepsy but the successful management of the patient with a convulsive disorder depends on the ability of the physician to prevent the occurrence of seizures The most effective treatment for the control of seizures is the use of anticonvulsive drugs phenobarbital diphenylhydantoin sodium (dilantin sodium) methylphenylethylhydantoin (mesantoin) phethenylate sodium (thiantoin) tridione paradione and the bromides At the present time ketogenic diet and dehydration are used very little because of the difficulty in maintaining the diet and the discomfort that results from dehydration

Certain drugs are more effective in one type of seizure than they are in another and it is necessary to vary the drug and the dosage for the different kinds of seizures If satisfactory results are not obtained by one of the drugs the others should be tried but frequent shifting of drugs is not advisable and each should be given an adequate trial before another is substituted In some patients a combination of two or more drugs will produce much better results than the use of one alone The therapeutic dose

indicated also in patients with acute infections with liver disease or with avitaminosis particularly vitamin C deficiency There is some doubt as to whether pregnancy is a contraindication for the use of ergotamine tartrate but it probably should be avoided at this time if possible

Prolonged usage over a longer period of time may lead to ergotism so that no more than 0 5 mg parenterally or 12 mg by mouth should be given in twelve hours The development of paresthesias numbness coldness and absence of vascular pulsations in the extremities prohibits further use of the drug Undesirable side effects such as nausea and vomiting occur in over half the patients when the medicine is given intravenously Atropine will alleviate these symptoms Calcium gluconate can be used to relieve the muscular pains which develop in a small number of patients after treatment Symptoms such as substernal oppression weakness and drowsiness occasionally follow the administration of the drug but are not a contraindication to its use

Dihydroergotamine methanesulfonate (D H E 45) is said to produce less side effects than ergotamine tartrate It is most effective when given parenterally in a dose of 1 mg (1 cc) at the onset of the headache This dosage may be repeated in one to two hours if necessary The same contraindications apply to the use of this compound as to ergotamine tartrate

MENIERE S SYNDROME

This syndrome is characterised by recurrent attacks of severe vertigo accompanied by nausea and vomiting Most patients with Ménière s syndrome also complain of tinnitus in one or both ears and progressive deafness These symptoms are usually more severe during an attack but are present between attacks An attack may last from a few hours to a day or more and the frequency may vary from several a week to one in several years

Treatment

The only treatment which assures permanent relief from the recurrent attacks of vertigo is surgical destruction of the labyrinth or of a section of the vestibular branch of the eighth nerve on the affected side While this will prevent the occurrence of subsequent attacks of vertigo it will not as a rule abolish the tinnitus Since however good results have been obtained by medical treatment it is best to try the latter before resorting to surgery

Several methods of medical treatment have been advocated for this condition It is difficult to evaluate the efficacy of any particular method of treatment because of the spontaneous variations in the frequency of the attacks

Potassium Chloride This is probably the easiest form of treatment It consists of the oral administration of 8 Gm of potassium chloride daily in the form of a 25 per cent aqueous solution 4 cc teaspoonfuls four times a day If gastric distress is produced by the use of the aqueous solution the potassium chloride can be given in enteric coated tablets Large doses of potassium are contraindicated in patients with kidney disease associated with nitrogen retention in the blood

Salt Free Diet and Ammonium Chloride This treatment consists of the administration of large amounts of ammonium chloride and a diet entirely salt free with avoidance of all substances containing sodium Ammonium chloride (9 Gm) is given daily in the form of capsules Each capsule is equal to 0 5 Gm and 6 are given three times a day at mealtime The medication is given for three days and then omitted for two days for an indefinite period of time

Nicotinic Acid This form of treatment usually is recommended for elderly patients with arteriosclerosis or those in whom vas-

nervousness and unsteadiness of gait are frequently transient appearing usually during the first few days of therapy and disappear with the continuation of therapy or with a temporary reduction in dosage The presence of nystagmus and ataxia calls for a temporary or permanent reduction of losage The reduced dose may not be ef ective in controlling the seizures and in such instances a combination of diphen ylhydantoin sodium and phenobarbital should be tried

Giving the drug at mealtime or with a little bicarbonate of soda may control the gastrointestinal disturbances The dermatitis which is accompanied by fever is of a scarlatiniform or morbilliform nature and usually occurs within two weeks of instituting therapy in about 5 to 10 per cent of patients The appearance of the rash is an indication for discontinuing the drug Further use of the medicine is contraindicated if the rash recurs when treatment is reinstituted

Hypertrophy of the gums is one of the most troublesome and annoying toxic ef cts of the drug It is more common in ildren and varies from a slight swelling the gums to a marked hyperplasia with almost total covering of the teeth The elling can be retarded by massaging the ns daily Some patients report a reduc n in the gum hypertrophy by the use of um in the form of the lactate or glu te 3 Gm daily Any excessive growth m tissue can be excised by the dentist *thylphenylethylhydantoin* (mesantoin) rketed in the form of 0 1 Gm tablets toin like diphenylhydantoin sodium l in the treatment of grand mal and motor seizures and occasionally is ffective than other drugs in control ese seizures Relatively large doses ured (0 4 1 0 Gm daily) This drug administered in combination with n sodium and or phenobarbital *oxic side-effects* of mesantoin are similar to those of phenytoin sodium except that it does not produce gum hypertrophy It has more sedative effects than diphenylhydantoin sodium and a few cases of fatal blood dyscrasia have occurred Patients taking mesantoin should have monthly blood counts and be examined regularly

Phethenylate sodium (*thiantoin*) is dispensed in capsules of two sizes 0 13 Gm (white capsule) and 0 26 Gm (pink capsule) This compound is occasionally effective when diphenylhydantoin sodium and/or mesantoin have failed Fairly large doses are necessary 0 52–1 4 Gm daily, particularly when the drug is used alone It can be given in combination with diphenylhydantoin sodium mesantoin, and/or phenobarbital However when given with diphenylhydantoin sodium the side-effects of the latter compound may appear or be accentuated If it is desired to give thiantoin an adequate trial in such patients it is necessary to slowly decrease the dose of diphenylhydantoin sodium

The side effects of thiantoin are similar to those of diphenylhydantoin sodium and consist of itching sensations ataxia nystagmus dizziness diplopia and nausea and vomiting

Tridione (trimethadione) is distributed in capsule (0 3 Gm), tablet (0 15 Gm) and solution (0 15 Gm in each 4 cc) form It is effective when used in the treatment of petit mal It has no value in the control of grand mal or psychomotor seizures and when patients have one of the latter types of seizures as well as petit mal diphenylhydantoin sodium or phenobarbital should be combined with the tridione

The dosage of tridione for the treatment of petit mal varies from 0 3 to 2 0 Gm daily starting with 0 3 Gm and gradually increasing the dose until the seizures are controlled or evidence of toxicity appears

The *toxic effects* of tridione are photophobia skin rashes nephrosis and pancy

Vascular Diseases

CEREBRAL VASCULAR ACCIDENTS (APOPLEXY, STROKE)

Cerebral vascular lesions are the most common cause of generalized or focal disturbances of the brain The common types of cerebral vascular lesions, in order of frequency, are cerebral thrombosis, cerebral hemorrhage, primary subarachnoid hemorrhage, and cerebral embolism The first two make up the major part of these types of lesions The general clinical picture may be similar and it is often quite difficult to determine the nature of the lesion from the clinical data in any individual case The manifestation at the onset of the vascular accident may include headache, vomiting, convulsions and coma These symptoms, particularly coma occur more frequently in patients with cerebral hemorrhage than in the other types of cerebral vascular lesions A large hemorrhage or occlusion of a major vessel usually leads to an elevation of the temperature, an increase in the pulse rate, and an alteration in the rate and depth of respiration although these changes may not be noticed with a small lesion In patients with an intracerebral or primary subarachnoid hemorrhage, there almost always is stiffness of the neck caused by the presence of blood in the cerebrospinal fluid (meningeal irritation)

Signs of focal brain damage, such as hemiplegia, aphasia, and hemianopia, are related to the site of the lesion Mental symptoms and signs—confusion, disorientation and impairment of memory—frequently are present in the period immediately following a cerebral vascular accident It is not uncommon to find a transient hyperglycemia and glycosuria, particularly in patients with cerebral hemorrhage

The examination of the cerebrospinal fluid is of great value in the diagnosis of cerebral vascular lesions, and it may help distinguish the different types of lesions The cerebrospinal fluid pressure is usually normal or only slightly elevated in patients with a cerebral embolus or thrombosis Pressures between 200 and 300 mm are present in a small percentage of cases but readings greater than 300 are rarely seen In contrast, the pressure is greater than 200 mm in the majority of the patients with an intracerebral or primary subarachnoid hemorrhage The fluid is bloody in all cases of primary subarachnoid hemorrhage, in 75 per cent of the cases of cerebral hemorrhage, and in 15 per cent of the cases of cerebral embolism It is clear in cerebral thrombosis, although there may be a slight xanthochromic tinge with a few red blood cells on microscopic examination

Treatment

The treatment of patients with cerebral vascular accidents is divided into two parts First, the treatment in the immediate period after onset, which is mainly directed toward saving the life of the patient, and second, the treatment of residual defects

Acute Stage Treatment during this stage is entirely symptomatic and supportive Skillful nursing care is essential The patient should be on his back in bed with his head slightly elevated and turned to one side Sideboards or restraining sheet should be used Fluids and liquid nourishment should be given by mouth if the patient is conscious otherwise glucose solution (5 per cent) can be given subpectorally or in the thighs or by the use of a nasal stomach tube An inlying catheter or tidal drainage may be necessary Enemas given daily or every other day will help avoid irritation of the skin resulting from fecal incontinence and will also help estab

cular spasm is believed to play a part in the etiology of the attacks. A total daily dosage of 0.4 Gm. of nicotinic acid is given by mouth. Treatment is begun by giving one 50 mg. tablet four times a day with gradual increase in dose over a period of weeks until the maximum of 0.4 Gm. is attained. This amount is maintained indefinitely.

Histamine. Histamine desensitization by either the subcutaneous or intravenous method has been recommended as a form of therapy for those patients with Ménière's syndrome who have a positive response to the histamine skin test. Desensitization by the subcutaneous method involves the subcutaneous injection of gradually increasing amounts of histamine every other day until the patient within two minutes after the injection develops a throbbing frontal headache and a flush which lasts for five minutes. Treatment is begun by injecting 0.05 cc. of 1:10,000 histamine acid phos phate followed every other day by doses of 0.075 cc., 0.1 cc., 0.15 cc., 0.2 cc. and 0.3 cc. with an increase by 0.1 cc. there fter until 1 cc. is given. This may be in eased gradually up to the point of re tion by the injection of increasing nounts of 1:1000 histamine acid phos ate. When a reaction occurs with a tain dosage the same dose is repeated l if there is no reaction an increased ount of histamine can be given. If ever a reaction again appears with the e dose the next lower dosage is con ed the maximum tolerated dose and it en at weekly intervals for one month. cond and third course of treatment ionally is given if there is a recurrence nptoms.

ensitization by the intravenous d involves the intravenous injection mg. of histamine acid phosphate di n 250 cc. of normal saline. This is given at the rate of 15 to 30 drops per minute depending on the patient's reaction. If a reaction occurs similar to that described for the subcutaneous method the histamine must be administered more slowly. A course of treatment consists of 15 injections and as many more injections as necessary.

"Dramamine" (Dimenhydrinate). Recently this compound has been found to have a favorable therapeutic effect in some cases of Ménière's syndrome. It should be given daily in doses of 50–100 mg. four times a day. Small amounts of benzedrine or dexedrine can be given to counteract the occasional drowsiness produced by dramamine.

Other Measures. Phenobarbital 0.1 Gm. can be given daily in one or divided doses. Simple superficial psychotherapy is of value in some cases. Patients should be encouraged to live as normal a life as possible. During an acute episode the patient should be kept in bed in a quiet darkened room. Parenteral fluids may be necessary if the vomiting is severe and prolonged.

Choice of Therapy. While it is difficult to evaluate the effectiveness of any type of treatment in Ménière's syndrome it is probably best because of its simplicity to begin with the use of dramamine. Should this prove to be ineffective, potassium chloride can be tried with the addition of a daily dose of phenobarbital. Nicotinic acid should be employed next if the first two have not proved to be successful. The salt free diet plus ammonium chloride has been effective in some cases but it is difficult to persuade patients to maintain the rigid diet. Good results have been reported with the use of histamine therapy but it has not always been possible for others to get the same results.

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lish bowel control Bed sores can be avoided by frequent changes of position and careful attention to the skin Bed sheets should be changed immediately when they are soiled by urine or feces Sedatives should be used cautiously and opiates avoided in the treatment of the restlessness and headache because of the danger of depressing the respiratory center and deepening the coma The prophylactic use of penicillin (450 000 units every twenty four hours) and frequent changing of the patient s position will help prevent the development of pneumonia Cyanosis and irregular respirations are indications for the use of oxygen and stimulants such as caffeine and sodium benzoate 0 5 Gm subcutaneously every two to three hours

A procaine block of the cervical sympathetics on the side of the lesion has been advocated as a method of producing improvement in some of the symptoms that result from cerebral vascular accidents The use of the anticoagulants such as dicumarol and heparin for the treatment of patients with cerebral thrombosis is still in experimental trial It is too early to evaluate the results obtained from both of these forms of treatment •

The increased intracranial pressure which often accompanies an intracerebral or subarachnoid hemorrhage can be treated by removal of fluid by lumbar puncture unlikely that removal of cerebrospinal will increase the bleeding and it may of considerable value in relieving the increased intracranial pressure especially a large amount of blood has been aspirated into the subarachnoid space lumbar puncture may be repeated at intervals of twelve to twenty four hours if amounts of bloody fluid can be re-[moved] At the time of each puncture suffi[cient flui]d should be removed slowly to re[duce the] pressure to half the initial reading [In so]me patients who have had intra[cerebral] bleeding the clot is slowly absorbed and may act like a tumor The diagnosis of such a lesion is difficult Those patients who have survived the initial shock of the hemorrhage and continue to show increased intracranial pressure should undergo surgery for evacuation of the clot Such operations have proved of lifesaving value in a number of cases and are of benefit in decreasing the severity of the neurologic defect

Patients with a primary subarachnoid hemorrhage are likely to have recurrences of bleeding The usual source of hemorrhage in such cases is a ruptured aneurysm Localization of the aneurysm sometimes can be made from the clinical picture but if this is not possible cerebral angiography should be utilized

There are two surgical procedures that will relieve the pressure on the aneurysmal sac The first is ligation of the internal carotid on the side of the aneurysm provided the patient does not develop a hemiplegia when the internal carotid has been occluded by manual compression for periods as long as twenty minutes The second method is to expose the aneurysm by craniotomy and ligate the vessel on both sides of the sac This latter operation is a major surgical procedure and is accompanied by a high mortality rate In most instances it would seem wise to defer surgery until there is evidence of one recurrence of bleeding

Convalescent Stage This period begins after the patient has recovered from the initial shock Treatment at this time is directed toward restoration of function in the paralyzed limbs Therapeutic procedures include the proper use of splints physiotherapy and muscle and speech training Splints are applied to prevent stretching of paralyzed muscles while the limbs are at rest Usually anterior splints to the forearm and posterior splints to the ankle joints are sufficient Physiotherapy is started as soon as the patient is strong enough •

• [See als]o Chapter 15

• See also Chapter 45

Light massage of the paralyzed muscles applied several times daily and passive movements of all the joints of the affected limbs are useful in maintaining the proper circulation and nutrition of the muscles and help prevent the development of arthritic changes in the joints The patient should be encouraged to try to use the paralyzed muscles and the first voluntary movements should be aided by simultaneous passive movements of the joints While the aid of a skillful physiotherapist is desirable relatives of the patient can be taught to manipulate all the joints of the paralyzed arm and leg for a few minutes several times a day The return of dexterity in the hands can be aided by giving the patient a rubber ball to squeeze With return of function more skillful actions should be tried No degree of paralysis should be considered hopeless and treatment should be continued for at least a year or two before abandoning hope of further improvement

Patients who have had a primary subarachnoid hemorrhage should be kept in bed until all the symptoms have disappeared and the cerebrospinal fluid is entirely normal Patients who have had the other types of vascular lesions are allowed to sit up in a chair for a few minutes possible and this is continued intervals each time the patient tempts at walking are initiated the patient walk with the help o ants The support of a crutch or substituted as soon as possible ar are discarded when the strength trunk and leg muscles is sufficient port the patient

Aphasia or *dysarthria* can be imp greatly by speech training Best result obtained when the re education is u the guidance of a trained speech therap If no therapist is available the physic can accomplish a great deal Constant p sistent efforts are required starting wi simple pictures and sound and graduall increasing the complexity of the symbol as the speech function returns It is best to begin the training as soon after the onset of the speech disturbance as possible but good results can be obtained even with patients who have been completely aphasic for many weeks or months

When the vascular lesion is caused by some underlying disease such as syphilis or subacute bacterial endocarditis appropriate therapy for these conditions should be given

Tumors

INTRACRANIAL TUMORS

The brain is one of the more common ites for the development of new growths s a source of neurologic manifestations tracranial neoplasms rank next to mul ple sclerosis in frequency The standard thod of classifying tumors is according their histologic nature Some idea of the tive frequency of the various tumors be obtained from Table 21 (modified Cushing)

e figure given by Cushing for metastatic tumors (four per cent) probably does not represent the true incidence because he worked in a specialized clinic in which such tumors were screened out In general hospitals the incidence of metastatic tumors is much higher and usually approximates 15 to 18 per cent

Diagnosis

The clinical manifestations of intracranial tumors are both general and local The general symptoms

lish bowel control Bed sores can be avoided by frequent changes of position and careful attention to the skin Bed sheets should be changed immediately when they are soiled by urine or feces Sedatives should be used cautiously and opiates avoided in the treatment of the restlessness and headache because of the danger of depressing the respiratory center and deepening the coma The prophylactic use of penicillin (450 000 units every twenty four hours) and frequent changing of the patient s position will help prevent the development of pneumonia Cyanosis and irregular respirations are indications for the use of oxygen and stimulants such as caffeine and sodium benzoate 0 5 Gm subcutaneously every two to three hours

A procaine block of the cervical sympathetics on the side of the lesion has been advocated as a method of producing improvement in some of the symptoms that result from cerebral vascular accidents The use of the anticoagulants such as dicumarol and heparin for the treatment of patients with cerebral thrombosis is still in experimental trial It is too early to evaluate the results obtained from both of these forms of treatment •

The increased intracranial pressure which often accompanies an intracerebral or subarachnoid hemorrhage can be treated by removal of fluid by lumbar puncture unlikely that removal of cerebrospinal will increase the bleeding and it may of considerable value in relieving the increased intracranial pressure especially a large amount of blood has been aspirated into the subarachnoid space lumbar puncture may be repeated at intervals of twelve to twenty four hours if amounts of bloody fluid can be re-At the time of each puncture sufficient should be removed slowly to re pressure to half the initial reading some patients who have had intra bleeding the clot is slowly absorbed and may act like a tumor The diagnosis of such a lesion is difficult Those patients who have survived the initial shock of the hemorrhage and continue to show increased intracranial pressure should undergo surgery for evacuation of the clot Such operations have proved of lifesaving value in a number of cases and are of benefit in decreasing the severity of the neurologic defect

Patients with a primary subarachnoid hemorrhage are likely to have recurrences of bleeding The usual source of hemorrhage in such cases is a ruptured aneurysm Localization of the aneurysm sometimes can be made from the clinical picture but if this is not possible cerebral angiography should be utilized

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• See also Chapter 13

• See also Chapter 45

hemisphere may prolong life from months to years Partial removal of pituitary tumors is indicated when vision is seriously compromised as the result of the compression of the optic chiasm or nerves by the tumor Many intracranial tumors (glioblastomas) grow so rapidly and are so malignant that most neurosurgeons will not attempt their removal The astrocytomas and polar spongioblastomas of the hemispheres are slow-growing tumors but usually are so widespread that they are not amenable to surgery Certain growths such as gliomas of the brain stem are so situated that they can not be approached surgically

Roentgen Irradiation Irradiation is the treatment of choice for patients with medulloblastomas of the cerebellum It is used in place of surgery in those cases of pituitary tumors in which vision is not seriously impaired In addition roentgen therapy is used postoperatively in all patients with infiltrating tumors of the brain This type of treatment should be carried out by a qualified roentgenologist

Other Treatment Many neurosurgeons give 0 1 Gm phenobarbital daily as a prophylactic measure to all patients who have been operated on for a supratentorial tumor This dosage is continued for a period of two years following the operation Should convulsions occur the dosage of phenobarbital may be increased or diphenylhydantoin sodium may be added or substituted for the phenobarbital as in the treatment of epilepsy

SPINAL CORD TUMORS

The meningiomas neuromas and intramedullary gliomas are the three most common types of spinal cord tumors In addition the spinal cord or roots may be compressed by cysts granulomas lymphomas ruptured intervertebral disks or by metastatic carcinoma and sarcoma The clinical manifestations of a tumor of the spinal cord are radicular pain and a spastic paresis of all the muscles and diminution of all forms of sensation below the level of the lesion Intramedullary gliomas may give a picture resembling that of syringomyelia There is usually a complete subarachnoid block at lumbar puncture with a moderate to marked elevation of the protein content of the cerebrospinal fluid Tumors involving the cauda equina give rise to root pains weakness of the lower extremities sphincter disturbances segmental sensory loss and a decrease or loss of deep reflexes As a rule no subarachnoid block can be demonstrated at lumbar puncture but the protein content of cerebrospinal fluid is elevated. Tumors of the cauda equina can be demonstrated by the subarachnoid injection of a contrast medium such as pantopaque or lipiodol

Treatment

As with intracranial tumors surgery and irradiation are the therapeutic measures used in the treatment of tumors of the spinal cord The meningiomas and neuromas are well encapsulated and can be removed at operation The degree of recovery after such an operation depends on the amount of damage that the underlying cord has suffered by the compression The intramedullary gliomas which are only rarely amenable to surgery are temporarily influenced by irradiation

TUMORS OF THE PERIPHERAL NERVES

Tumors of the peripheral nerves are rare and when they do occur they usually are part of the condition known as neurofibromatosis They may be solitary or multiple The tumor nodule may be painful and may produce paresthesias in some nerve distribution Associated with the tumors in neurofibromatosis there may be cutaneous pigmentation skeletal changes and visceral involvement

When the neurofibromas become painful or sarcomatous treatment consists of surgical excision of the tumor

TABLE 21 RELATIVE FREQUENCY OF INTRACRANIAL TUMORS

Tumor	Relative frequency (%)
Gliomas	43
Pituitary adenomas	18
Meningiomas	13
Acoustic neuromas	9
Congenital tumors (cariopharyngiomas cholesteatomas dermoids etc)	6
Metastases	4
Granulomas (tuberculomas syphilomas)	2
Blood vessel tumors	2
Miscellaneous	3
	100

ache vomiting papilledema and changes in the state of consciousness varying from drowsiness to coma are caused mainly by increased intracranial pressure The local symptoms are caused by destruction of brain tissue which results from invasion or compression by tumor tissue These are usually progressive and consist of such manifestations as impaired sense of smell isual difficulties aphasia hemiplegia or onvulsive seizures It is important to ote that headache vomiting and choked scs may be late symptoms of an racranial tumor and that increased racranial pressure may be entirely ab- when the tumor is in certain locations as the pituitary gland or the brain

Contrasted to this is the fact that tumors situated in the so-called silent of the brain such as the temporal on the nondominant side do not pro- ocalizing signs and may be manifested generalized convulsions and evi of increased intracranial pressure It ently difficult to make an accurate s of the type of tumor prior to n but some information regarding ogic characteristics can be deduced age of the patient and the rate of nd location of the tumor

Cerebrospinal Fluid. Examination o the cerebrospinal fluid is of great value in the diagnosis of brain tumors Lumbar puncture can be performed without any undue risk whenever there is no or only slight choking of the disks It should not be performed whenever there is a high degree of choking of the disks unless it is necessary in establishing the diagnosis At such times the puncture should be done by a neurologist or neurosurgeon Deter minations of the intracranial pressure and the protein content of the spinal fluid are of special value in the diagnosis of tumor In the majority of intracranial tumors one or both are elevated

In addition to the lumbar puncture there are a variety of special tests that are utilized in the diagnosis and localization of intracranial tumors These include roentgenograms of the skull electroen cephalography pneumoencephalography ventriculography and cerebral angi ography For the most part these tests should be done by a neurologist or neuro- surgeon

Treatment

Surgery and irradiation are the two measures used in the treatment of intra cranial tumors

Surgical Therapy Ideally once the diagnosis has been established a brain tumor should be removed surgically Un fortunately this can be done effectively in less than half of the cases Meningiomas acoustic neuromas pituitary adenomas and some cerebellar astrocytomas are par ticularly amenable to complete surgical removal However even though these tu mors are relatively benign and slow grow ing they may grow so large become so vascular and be so located that complete removal is often difficult In about one quarter of the cases radical removal of some of the tumors such as the cranio- pharyngiomas congenital tumors heman gioblastomas and some gliomas of the

be maintained If fluids and nourishment cannot be taken by mouth a nasal stomach tube should be utilized or the fluids given parenterally *Careful attention should be* given to care of the skin and the eyes should be protected from drying Bladder distention should be prevented by the use of an *indwelling catheter and bowel con* trol should be maintained by the frequent *use of enemas (daily or every other day)*

Analgesics such as acetylsalicylic acid 0 6 Gm can be given *as frequently as necessary* for headache, but morphine should be avoided The restlessness which is frequently present is a difficult symptom to treat It is best in such instances to have side boards applied to the bed rather than hav ing the patient put in restraints a procedure which usually increases the pa tient s straining Large doses of sedatives are to be avoided because of the danger of masking symptoms particularly changes in the state of consciousness If the patient is unduly restless he may be quieted by small doses of barbiturates or by rectal admin istration of paraldehyde in doses of 15–30 cc in 250 cc of starch solution Caffeine 0 5 Gm intravenously can be given as a stimulant if needed Penicillin in aqueous suspension in a dose of 300 000 units can be given intramuscularly once daily for five to seven days as a prophylactic measure in patients with severe head injuries

Increased intracranial pressure can be reduced by removal of cerebrospinal fluid by lumbar puncture or by dehydrating the patient *Dehydration can be accomplished* either by the use of hypertonic solutions—50 per cent of glucose in doses of 100 cc intravenously or 250 cc of a saturated solu *tion of* magnesium sulfate rectally—or by drastic limitation of fluid intake The re sults obtained by the use of these methods are somewhat uncertain and may if used over a long period of time produce a toxic degree of dehydration It probably is wiser to give patients an adequate fluid intake and control the intracranial pressure by removal of cerebrospinal fluid by lumbar puncture As mentioned before the first *lumbar puncture is performed* as soon as the patient has recovered from shock to aid in the diagnosis of the type of brain injury The intracranial pressure should be accu *rately measured and if elevated* sufficient fluid should be removed to reduce the pressure to a *normal level* The puncture should be repeated at intervals of eight to twenty *four hours until the pressure returns* to normal and the blood has been removed

Too frequently patients who have had a severe head injury are immediately rushed to the roentgenologic department for skull x rays Most often nothing is gained from such a procedure and usually valuable time is lost in the institution of rational therapy The presence or absence of a linear fracture of the skull is of no practical significance in the early management of the case Roent genograms however should be taken at some time before the patient is discharged from the hospital When the patient s con dition suggests the possibility of an extra dural hemorrhage roentgenograms of the skull are of definite value and should be taken as soon as possible

Convalescent Stage The rehabilitation of patients with cerebral injuries is of great importance in preventing the development *of posttraumatic syndromes or chronic* in validism A head injury is a frightening ex perience to the average patient *and* he usually has distorted ideas regarding the disastrous *effect of such* an injury While the seriousness of any damage to the nerv ous system should not be minimized care must be taken not to overemphasize minor injuries The patient should be reassured and if circumstances warrant should be told that there has been no significant dam age to his brain and that he will be per fectly normal within a short time Patients who have suffered a minor concussion are allowed out of bed in two to three days and

Trauma to the Nervous System

CRANIOCEREBRAL INJURIES

The intelligent treatment of head injuries may save many lives The majority of patients with head injuries have no injury to the skull except for a possible linear fracture This group makes up what is frequently called the closed head injuries Operative intervention usually is not indicated unless some complication arises

Closed Head Injuries

The most useful classification of closed head injuries is the one based on the degree of brain damage Uncomplicated head injuries can be divided into three subgroups concussion edema and congestion and contusion and laceration A diagnosis of concussion is made in those cases in which there has been a minor injury to the brain which caused a momentary loss of consciousness without any objective signs of cerebral trauma and without any abnormalities in the cerebrospinal fluid Edema and congestion imply a more serious injury to the brain with resultant increase in the intracranial pressure and interference with circulation In such cases the pressure of the cerebrospinal fluid is elevated The diagnosis of contusion and laceration signifies the most severe type of closed head injury In these cases the brain is bruised or torn with resulting hemorrhage into the subarachnoid space or substance of the brain *The cerebrospinal fluid in such cases* is bloody and under increased pressure Focal neurologic signs may or may not be present

The most common complications of skull and head injuries are extradural and subdural hematomas meningitis depressed and compound fractures osteomyelitis or infected wounds of the scalp aeroceles cerebrospinal rhinorrhea and arteriovenous aneurysms These complications require treatment of a specialized nature

Treatment

The treatment of closed head injuries is divided into general care of the patient in the immediate period following injury and rehabilitation during the convalescent stage

Acute Stage Therapy in this phase is entirely symptomatic and supportive All diagnostic and special surgical procedures are deferred until the patient recovers from shock Shock should be treated by placing the patient in a warm bed with the feet elevated and transfusion of 250 cc. of whole blood When the patient has recovered or if this complicating factor is not present a diagnostic lumbar puncture should be done If possible special nursing care should be secured because patients with severe head injuries are acutely ill restless and have to be carefully watched for possible development of complications requiring surgical intervention Such patients should have their pulse, rate of respiration and blood pressure recorded every half hour and their temperature taken every hour during the first few hours after the injury and after that at two-hour intervals for at least the first twenty four hours When present blood or cerebrospinal fluid should be wiped from the external ear but under no circumstances should the ear be irrigated or probed To prevent the aspiration of mucus in comatose patients the airways should be kept clear by the use of suction and when necessary oxygen should be supplied by a nasal catheter Temperature elevations that exceed 101° F should be treated by exposing the body surface the use of a fan alcohol sponges and ice-water enemas

A fluid intake of 3000 cc. a day should

bridement as soon as the patient is well enough to tolerate such a procedure Special technical details must be followed if the fracture extends into the frontal sinus Simple depressed fractures are treated by elevating the depressed fragment This is not an emergency procedure unless the depressed fragment is large and is injuring vital areas of the brain

Treatment of *infected scalp wounds or osteomyelitis of the skull* consists of drainage and excision of the infected tissues

Aerocele is a condition in which air is present in the cranial cavity and indicates a communication between the nasal cavities and the intracranial spaces as the result of tears in the dura Roentgenograms of the skull will reveal the presence of the extraneous air The air may disappear spontaneously but if it does not the tear in the dura should be repaired surgically to prevent the development of meningitis

Arteriovenous aneurysm results from the formation of a fistula between the carotid artery and the cavernous sinus caused by injury to the carotid artery It is manifested clinically by the complaint of a roaring noise in the head and the presence of proptosis of the eyeball chemosis of the conjunctiva and lids and a loud murmur over the temples synchronous with the pulse Treatment consists of training the patient to compress his carotid artery for increasingly longer periods of time until it has been shown that a sufficient collateral circulation is present This is then followed by ligation of the internal and common carotid artery on the side of the fistula

INJURIES TO THE SPINAL CORD

The spinal cord or roots of the cauda equina may be injured by perforating missiles traumatic hemorrhages, or by compression as a result of fracture dislocation of the spine The clinical manifestations depend on the location and extent of the lesion, and are usually a combination of paralysis and sensory loss below the level of the lesion, with loss of control of the bladder and rectum Spinal shock is usually present immediately following an injury to the cord for a period of hours to months During the period of spinal shock it is impossible to determine accurately the neurologic deficit of the patient

Treatment

Transportation of the patient from the scene of injury to a hospital should be carried out with great care Patients with a suspected spinal cord injury should not be moved until adequate facilities are available to ensure complete immobility of the spine Flexion of the spine should be absolutely avoided and the patient carried only in the prone position on a firm support with traction on the neck When the injury is in the cervical region, the neck should be kept in extension and the traction maintained by the application of suitable apparatus as soon at the patient enters the hospital Fractures of the thoracic or lumbar region can be immobilized by the application of suitable casts Movement of the patient should be kept to a minimum and only such diagnostic procedures as a lumbar puncture and roentgenograms of the spine should be made These are of importance to help determine whether the symptoms are due to cord compression by a fracture dislocation or whether they are the result of hemorrhage into the cord The presence of complete or incomplete dynamic block on lumbar puncture is evidence which points to cord compression and is an indication for laminectomy to relieve the compression

Care of the skin and the bladder are of extreme importance in the first few weeks or months after an injury to the spine Careful nursing care is essential to avoid the development of bed sores The bed must be kept clean and dry at all times and

are discharged from the hospital within five days They should be encouraged to return gradually to their usual activities after a few days rest Patients who have suffered more severe brain injuries should have a longer period of hospitalization and convalescence at home Such patients should not be allowed out of bed until the cerebrospinal fluid pressure has been kept at a normal level for several days They should be discharged from the hos pital when they are able to walk up and down two flights of stairs without difficulty The patient should be informed that since he is able to perform such activity the chance of his becoming a chronic invalid at home is minimal A *schedule of activities* should be prescribed which includes some regular exercise such as short walks or light work around the house Patients with moderately severe injuries should return to part time work in three to four weeks after discharge from the hospital and to full time work within three months The period of convalescence should be three to six weeks longer for the most severe in juries During this time the patient should be encouraged to follow a normal routine of living but the use of alcohol should be prohibited

Treatment of the Complications of Head Injuries The treatment of many of the complications of head injuries is primarily surgical and should be carried out by a competent neurosurgeon

The diagnosis of *extradural hematoma* is based on the occurrence of a certain se quence of events An injury to the head accompanied by coma followed by a recov ery of consciousness and a subsequent lapse into coma coincidental with the develop ment of a hemiplegia Roentgenographic evidence of a fracture line running through the groove of the middle meningeal artery or one of the larger cerebral venous sinuses confirms the diagnosis When this picture is present the diagnosis is not difficult how ever, it is only present in a little more than half the cases Treatment is immediate oper ation with evacuation of the clot and liga tion of the bleeding vessel Early diagnosis and immediate treatment will result in com plete recovery in many cases undue delay will almost invariably result in death

Subdural hematoma should be suspected in all patients who do not respond to routine treatment, especially if focal neurologic symptoms develop or get worse or if there are alternating periods of stupor and consciousness Roentgenograms of the skull may help in the diagnosis if there is evidence of a shift of the pineal gland The only accurate method of diagnosis is by surgical exploration This is not a difficult procedure and is fairly well toler ated by even severely ill patients Small trephine holes are made in the temporal region on both sides and if a hematoma is present it is evacuated by suction

A chronic subdural hematoma should be suspected whenever focal neurologic signs and symptoms of increased intracranial pressure develop within a few weeks or months after a head injury Roentgen ograms of the skull pneumoencephalog raphy and electroencephalography are sometimes of diagnostic aid but the diag nosis can be excluded only by surgical ex ploration as described above

Any of the pathogenic bacteria may pro duce a *meningitis* following head injury The development of an inflammatory re action in the cerebrospinal fluid establishes the diagnosis The treatment is the same as that previously outlined in the section on meningitis

Brain abscess secondary to fracture of the skull is treated by chemotherapy and sur gery in a manner similar to that for ab scesses from other sources.

A diagnosis of *compound fracture of the skull* is made by palpation of the skull through the lacerated scalp Treatment consists of chemotherapy and surgical de

bridement as soon as the patient is well enough to tolerate such a procedure Special technical details must be followed if the fracture extends into the frontal sinus Simple depressed fractures are treated by elevating the depressed fragment This is not an emergency procedure unless the depressed fragment is large and is injuring vital areas of the brain

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Care of the skin and the bladder are of extreme importance in the first few weeks or months after an injury to the spine Careful nursing care is essential to avoid the development of bed sores The bed must be kept clean and dry at all times and

the patient should be turned frequently When available sponge rubber mattresses *should be used instead of the ordinary hair* mattresses since they are less likely to produce the pressure sores which are then followed by the development of bed sores The use of a constant drainage apparatus for the bladder will prevent soiling of the bed and maceration of the skin by urine It also will help to prevent the almost inevitable cystitis and ascending urinary infection and when properly regulated will *hasten the return of bladder function* The antibiotics and/or chemotherapy are indicated when there is evidence of infection

Efforts must be made to obtain the maximum return of function in the partially paralyzed extremities by the use of physiotherapy massage passive movements and muscle training

Neuroses

IT HAS been estimated that about 50 per cent of patients who consult a physician do so because of functional illness and that about 12 to 30 per cent of all general hospital admissions are eventually discharged with a diagnosis of a functional disorder Obviously even in large cities there are not enough psychiatrists to treat this sort of a patient load and in many smaller communities there are no psychiatrists at all Fortunately in many instances the problems are so mild or so minor that the physician who is not a psychiatrist can handle them At times the general practitioner is the one most eminently suited to treat such cases because of his personal knowledge of the family background and the environment in which the patient lives *

There are a variety of syndromes that are classified under the heading of neurosis or psychoneurosis One of the simpler classifications is the following

1 Anxiety neurosis
2 Conversion hysteria
3 Neurasthenia
4 Obsessive-compulsive states

While these syndromes can be distinguished there is frequently an overlapping of symptoms Such cases are sometimes referred to as mixed neuroses Basically the neuroses are the symbolic conscious manifestations of unresolved emotional conflicts that occur in the unconscious mind The particular syndrome that is manifested and the mechanisms by which it is produced are determined largely by the individual personality

* See also Chapter 25

ANXIETY STATES (ANXIETY NEUROSES)

This is most common of all the neurotic syndromes anxiety is the predominating symptom This condition is manifested by frequent attacks of acute anxiety palpitation choking sensations marked sweating tremor of the face and hands and nameless fears Such attacks may last from a few minutes to several hours or days and often occur at night Patients with anxiety neuroses are frequently tense apprehensive and irritable Many find concentration difficult and phobias of all kinds are common There may be a variety of somatic symptoms

CONVERSION HYSTERIA

The symptoms of *conversion hysteria* usually appear abruptly and dramatically The clinical picture may vary greatly and includes such manifestations as amnesia

confusional states seizures blindness deafness aphonia paralyses abnormal movements tics nausea and vomiting anorexia nervosa and pseudocyesis Despite the apparent severity of the symptoms the patient with conversion hysteria usually shows little or no concern

NEURASTHENIA

In this form of neurosis the outstanding symptoms are marked physical and mental fatigue Associated with these symptoms there are frequently complaints of headache inability to concentrate irritability and a variety of visceral difficulties

OBSESSIVE AND COMPULSIVE STATES

This is probably the most severe type of neurosis and the one most difficult to treat This condition is manifested by obsessional ideas and compulsive conduct either alone or together Obsessional ideas are persistent thoughts frequently concerned with religion or death which occupy the consciousness without the conscious will of the individual Usually there is so much doubt and indecision about the thought that it is never carried into action Compulsions are usually the ritualistic repetitions of some act which varies from patient to patient and which increases in complexity as the illness continues Examples of compulsions are repeated hand washing special rituals in dressing and undressing and the manias such as dipsomania kleptomania and pyromania

TREATMENT

The treatment of the neuroses is psychotherapy This signifies any method which attempts to change the thinking and emotions of the patient regarding himself his illness and his interpersonal relationships Psychotherapeutic measures can be divided into two groups The first group can be described as palliative supportive or nontechnical therapy and can be utilized by the nonpsychiatric physician The second group consists of the technical more formal measures used by the psychiatrist

Nontechnical Psychotherapy

There are many things that the physician can do to help the patient with functional illness Levine has listed thirty methods that can be utilized by the general practitioner It is essential that the physician be sympathetic and understanding and that he develop rapport with the patient An understanding of the patient and his problems will contribute a great deal to the success of the treatment

A few of the more common methods will be discussed here briefly

Examination A complete history and physical examination with the addition of the necessary laboratory tests are important not only diagnostically but also psychotherapeutically The thoroughness of the examination plus a definite statement by the physician that there is no evidence of organic disease can in many mild cases relieve the anxiety arising over the fear of such diseases as cancer and syphilis In addition the correction of any concomitant physical disability revealed by the examination may be of value The anxiety regarding bodily illness may recur in a different form in some patients but the remissions may be lengthy

Information, Reassurance and Encouragement Many patients have accumulated a great deal of misinformation regarding disease processes and as the result of misinterpretations develop anxiety and fear As mentioned above a thorough examination is an excellent method of reassurance Correction of misinformation by adequate explanation in lay terms frequently will relieve the symptoms arising from the fear of inheriting mental disease cancer diabetes and hypertension Some patients with minimal symptoms of mild organic

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hile these syndromes can be distin d there is frequently an overlapping nptoms Such cases are sometimes referred to as mixed neuroses Basically, the neuroses are the symbolic conscious manifestations of unresolved emotional conflicts that occur in the unconscious mind The particular syndrome that is manifested and the mechanisms by which it is produced are determined largely by the individual personality

ANXIETY STATES (ANXIETY NEUROSES)

This is most common of all the neurotic syndromes anxiety is the predominating symptom This condition is manifested by frequent attacks of acute anxiety palpitation choking sensations marked sweating tremor of the face and hands and nameless fears Such attacks may last from a few minutes to several hours or days and often occur at night Patients with anxiety neuroses are frequently tense apprehensive, and irritable Many find concentration difficult and phobias of all kinds are common There may be a variety of somatic symptoms

CONVERSION HYSTERIA

The symptoms of conversion hysteria usually appear abruptly and dramatically The clinical picture may vary greatly and includes such manifestations as a

* ho Chapter 25

While ventilation is an effective means of psychotherapy in many patients, it is a time consuming procedure. Patients are quick to resent being cut off in the middle of a confidence and to them it implies lack of interest on the part of the physician. If this type of therapy is to be used the physician should plan his time accordingly.

Changing the Patient's Environment. Environmental or situational difficulties can produce emotional problems in many individuals. The loss of a job, failure to get a promotion, excessive responsibility, economic burdens, domestic quarrels over protective or disinterested parents and a variety of other stress producing situations can give rise to neurotic symptoms. In such instances the physician must do everything possible to remove or change these external strains. It may involve modifying the patient's routine of life, curbing his ambitions, working with the family and employer, and utilizing available social agencies.

No one particular method of psychotherapy may be effective by itself and usually a combination of many methods is necessary. It is evident that none of these methods removes the basic causes of the neurosis, but their removal is not always necessary. If the physician by sympathy, understanding, common sense and the use of nontechnical psychotherapeutic measures can keep the patient relatively happy, moderately well adjusted and economically sufficient, treatment has been successful. When the physician has been unable to do these things, referral to a psychiatrist is indicated.

Technical Psychotherapy

This type of psychotherapy aims to remove the underlying, deep rooted causative factors of the neurosis and is the province of the specialist in psychiatry. The technics utilized are highly specialized and include such methods as psychoanalysis and its various modifications, such as short term analyses, child analysis and individual play therapy, hypnosis, hypnonarcoanalysis and distributive analysis.

Psychoanalysis. To many people psychoanalysis and psychiatry are synonymous terms. Actually psychoanalysis is only one school of thought in psychiatry, established and developed by Sigmund Freud and his followers. In its orthodox form it is the method of treatment used by psychiatrists who have been specially trained in and who follow the teachings of this school. Psychoanalytic therapy is essentially an uncovering technic. It attempts to bring into the conscious mind many of the early childhood experiences that psychoanalysts believe are not forgotten but remain in the unconscious where they act as a dynamic force in the production of symptoms. The purpose of psychoanalytic therapy is to explore these unconscious factors and to determine which ones are responsible for the neurotic difficulties. This is done by means of free association, by which the patient verbalizes in an undirected fashion all thoughts and phantasies and the associations they provoke. After a period of time the analyst becomes a symbol of people previously important to the patient. As the repressed memories with their associated emotional content are brought into consciousness the patient directs toward the analyst all the emotions associated with the individual whom the psychoanalyst symbolizes. This is known as the process of transference. Eventually the analyst interprets to the patient the meaning of certain experiences and the significance of certain of the patient's reactions to those experiences. By means of psychoanalysis the patient is given an understanding of and an insight into his fundamental difficulties. It is essentially a reshaping of the entire personality so that environmental stresses are met without symptom formation.

Psychoanalysis is a time consuming

illnesses or with mild depression are con vinced that they are seriously ill or that they are developing a chronic, incapacitat ing disease Reassurance in such cases can do much to relieve the functional overlay and promote a more healthful outlook It must be understood however that reassur ance as a means of psychotherapy is a very superficial method and the physician must not expect too much from it Its particular value is in the treatment of superficial anxieties and its failure may well be an indication that the anxieties are deep seated and in need of a more technical type of psychotherapy

Suggestion The effectiveness of this type of therapy is based partially on the author tative position of the physician and in art on the fact that many people are ggestible a trait that is present to an aggerated degree in many neurotic in iduals This accounts for the improve ment that results from the use of placebos injections and manipulative therapy There are many forms of suggestive ther apy such as electrical stimulation of paralyzed muscles in hysterical individuals the use of placebos the giving of some medications with appropriate impressive ness vocal suggestions and hypnosis It is evident that this is not a method of therapy that removes the basic cause of the diffi culty but in many cases it provides enough symptomatic relief to enable the patient o function effectively

Persuasion and Re education This thod of therapy utilizes the intelligence the patient The physician can in some s convince the patient that his symp are due to certain psychologic factors not to organic disease In this way the nt is made to understand his symp nd why it is unnecessary for him to hem This method requires excellent between the physician and the and as can be expected can only n a select number of patients

Re-education therapy consists of the patient the necessity of modify trolling, or releasing certain of pulses It demands voluntary effort part of the patient and, at times a bl of his tendency to self criticism In cases particularly those with mild pho the patient can be taught that the antic tion of a fear is greater than its realizat and by this method is enabled to face ma of his fears With the help and encourag ment of the physician the patient actual faces and carries out the situation tha produces the fear

Recreation This type of therapy should be attempted in those patients who are markedly preoccupied with their problems and are ineffectual in solving them It in cludes essentially the establishing of such outside interests as hobbies sports garden ing the theatre movies and cultural proj ects It should be an activity from which the patient may gain a certain amount of enjoyment and release from his anxieties The physician who knows the facilities of his community may devise or suggest a number of ways by which the patient can secure a certain amount of diversion or recreation Long weekends occasional vaca tions or a day off may help relieve monotony and lessen tension

Confession and Ventilation This is an age old method of releasing tension The relating of certain unpleasant thoughts problems and worries to a sympathetic and understanding physician can produce a remarkable feeling of relief in the patient particularly if the physician's attitude is a noncondemning uncritical one If reassur ance and encouragement are utilized at the proper time during the period of catharsis much can be done for the patient The physician must constantly be aware of the fact that the material released by the patient may be indicative of a deep rooted functional illness Such patients should be referred to a psychiatrist for treatm

depressive psychoses and involutional melancholia Another rare form is paranoia The management and treatment of these diseases should be under the direction of a competent psychiatrist The shock therapies psychosurgery and psychotherapy are methods of treatment for these conditions It has been shown that the indicated type of shock therapy will vary with the specific form of the psychosis hence the importance of an accurate diagnosis prior to treatment

Schizophrenia

This form of mental illness is the commonest cause for admission to mental hospitals Schizophrenia is a disease of young people characterized by a dissociation of the intellectual and emotional activities marked introversion and sometimes complete withdrawal from reality to an inner phantasy existence complete with hallucinations and delusions and regression or retreat to an infantile mode of thinking Four types of schizophrenia are recognized

Simple Type This form is characterized by apathy indifference, blunting of emotions and progressive mental deterioration Hallucinations and delusions usually are not present

Hebephrenic Type This form is marked by mental deterioration and incoherence of thought These patients appear to be extremely silly giggle inappropriately and are markedly dilapidated They are constantly hallucinating and have bizarre delusions

Catatonic Type The typical symptoms in this form are the irregularly alternating periods of excitement and stupor During the period of excitement there is marked overactivity during which the patient seems to be reacting to his hallucinations and delusions Catatonic stupor is the most marked type of withdrawal In this state the patient remains entirely mute and fixed in one position There is bladder and bowel incontinence and nourishment must be maintained by a nasal stomach tube

Paranoid Type In this form the patient apparently maintains a fairly close contact with reality but his behavior is marked by extreme suspiciousness and there are usually delusions, hallucinations and ideas of influence and reference

Treatment

Insulin shock therapy is the treatment of choice for the paranoid type of schizophrenia and, to a lesser extent for the catatonic type It has its least value in the treatment of the simple and hebephrenic types When given during the first six months of the illness treatment will produce a remission or recovery in fifty to sixty per cent of the patients, as compared to ten to twenty per cent of spontaneous remissions in untreated cases

Insulin Shock Therapy This type of treatment must be given in a hospital by a psychiatrist experienced in the technic who has the help of trained personnel Essentially it consists in the production of coma by the use of insulin Treatment is begun with an initial dose of 20 units of insulin intramuscularly and the amount is gradually increased by 10 units daily until coma is produced The amount of insulin necessary to produce coma varies from patient to patient The patient is kept in a coma from thirty to ninety minutes before he is aroused by the administration of a solution of glucose by nasal stomach tube While in coma the patient must be watched very carefully A period of coma is produced six days a week until a course of about 50 comas has been administered The course of therapy may be repeated in those patients who have shown some improvement but have not fully recovered at the end of the first course or in those who have recovered and then develop a relapse The catatonic type of schizophrenia probably

method of therapy requiring treatment five days a week for a period of eighteen months to three years As a form of treatment it is indicated for most of the neuroses that appear in relatively young fairly intelligent patients particularly when other forms of therapy have failed Not every patient can be analyzed and it is for the psychoanalyst to decide which patient will benefit from this type of therapy

Hypnosis This is a method of psychotherapy which involves the technique of producing a state in which the patient is more suggestible than in the normal waking state Under hypnosis the patient in some instances is more amenable to curative suggestions thus it is a method of removing hysterical symptoms While under hypnosis patients at the command of the psychiatrist frequently are able to recall experiences which they are not aware of in their waking state The uncovering of such repressed material may have a therapeutic effect It is particularly effective in cases of hysterical amnesia This method has many of the difficulties inherent in suggestion therapy and is symptomatic treatment primarily

Hypnoanalysis This is a method of psychotherapy which combines hypnosis with the principles of psychoanalysis In the hypnotic state the patient brings u forgotten past experiences with their accompanying emotions While still under hypnosis the physician interprets to the patient the meaning of some of these experiences and the patient s reaction to them Interviews are carried out during the waking state in which the forgotten material is discussed with the patient

When sedative drugs are used to make the patients more accessible to hypnosis the method is known as hypnonarco analysis

Distributive Analysis This form of psychotherapy in contrast to psychoanalysis places major emphasis on environmental factors and conscious conflicts In a series of interviews a careful evaluation is made of all factors physical and mental that have occurred in the patient s life and that have contributed to the shaping of his personality Attempts are made to point out how certain experiences and personality traits can be related to particular nervous symptoms It includes such therapeutic measures as ventilation reassurance guidance persuasion and re-education It is a simpler treatment than psychoanalysis and is applicable to a larger number of patients

Psychoses

W therapeutic methods have produced ouraging results in the treatment of hoses This has in many cases done with the necessity of prolonged cus l care particularly in the group of lers known as the functional psy Unfortunately equally good results not been obtained in the treatment organic psychoses although the use icillin and malaria (fever) therapy ulted in the improvement and recovery of many cases of general paresis At the present time however there is no adequate therapy that will affect the mental symptoms resulting from the structural changes in the brain caused by old age and chronic vascular disease *

THE FUNCTIONAL PSYCHOSES

The psychoses commonly classified under this heading are schizophrenia manic

* See also Chapter 23

period of treatment may be necessary in complicated cases A short course of treatment may be repeated in those patients who develop a relapse This form of therapy preferably is given only to hospitalized patients

The presence of severe cardiovascular disease, thyrotoxicosis, peptic ulcer, acute infections, and pulmonary tuberculosis are contraindications to the use of convulsive shock therapy The most frequent complications of the treatment are compression fractures of spine the thoracic vertebrae being most frequently involved When they do occur they rarely give rise to serious difficulties and as a rule they do not produce spinal cord involvement or postural disturbances

The results of treatment by electroshock therapy of the manic phase of manic depressive psychosis are less favorable than those obtained in the depressive phase Patients in the manic phase of manic depressive psychosis are best treated in a mental hospital where various types of hydrotherapy are available When such patients are seen prior to hospitalization, sedation may be indicated to control their excitement and overactivity One of the safer and more effective sedatives is paraldehyde Large doses may be necessary 4–16 cc by mouth or 16–32 cc in 250 cc of starch solution rectally In those patients who are extremely difficult to control it may be given intramuscularly in a single dose of 10–15 cc The use of sedatives is a temporary measure until the patient can be hospitalized

Psychosurgery

More recently a variety of neurosurgical procedures have been devised for the treatment of some of the chronic, refractory types of functional psychoses These operative procedures have been helpful at times and often distressing mental symptoms have been removed so that the patients become more manageable Prefrontal lobotomy was the first of the operations devised The operation essentially consists of severing the connections between the frontal lobes and the thalamus by cutting into the white matter containing the fibers that connect these two regions Cerebral hemorrhage and the development of convulsive seizures are complications of this operation Various attempts have been made to reduce the incidence of these complications and to minimize the alterations of personality that occur after lobotomy by other types of operations Topectomy is one such surgical procedure which involves the removal of small areas of gray matter from the prefrontal regions (Areas 9 and 10) bilaterally Thalamotomy, a procedure which consists of placing destructive lesions in the dorsal medial nucleus of the thalamus bilaterally is another such attempt Transorbital lobotomy a modification of prefrontal lobotomy is still another type of operation that has been tried

The questions as to which type of patient should have psychosurgery and which particular operation to use are far from settled In general, it may be said that this is a radical type of treatment that should be considered only after all other therapeutic procedures have failed Good results have been reported in some cases of paranoid and catatonic schizophrenia in that the violent behavior and the destructive tendencies of the patients disappeared and they became more manageable Psychosurgery has been effective in some cases of severe refractory, obsessive-compulsive neuroses involutional melancholia, chronic phases of manic depressive psychoses and in some of the chronic depressions of old age

ACUTE (TOXIC) PSYCHOSES

Acute psychotic episodes are seen as symptomatic manifestations of transient and reversible central nervous system involvement in many medical conditions

responds best to a combination of insulin coma and electroshock

The contraindications to insulin shock therapy are acute infections pulmonary tuberculosis severe cardiovascular disease diabetes mellitus and other serious endocrine disorders The most serious complication of the treatment is protracted coma, and about one per cent of patients die as the result of the encephalopathy produced by the prolonged hypoglycemic coma

Manic Depressive Psychosis

This is one of the more common types of mental disease It is the cause of about 11 per cent of the admissions to mental hospitals patients in the depressed phase are not infrequently seen in the general practitioner s office with a variety of somatic complaints that mask the depression The outstanding clinical feature is the mood disturbance In the manic form there is marked elation excitement excessive uncontrolled activity and flight of ideas This form may occur alone or it may alternate directly, or after a period of normalcy with a period of depression In the depressed phase of the illness the patient is depressed retarded underactive or markedly agitated The in ensity of the depression varies and it may be so severe that the patient becomes a definite suicidal risk

Involutional Melancholia

A wide variety of symptoms are manifested in both males and females during the involutional period These may vary from mild emotional changes and hypochondriasis to a psychosis characterized by a severe form of depression with many anxiety symptoms paranoid thoughts and agitation This psychosis is known as involutional melancholia Patients with this form of mental illness are considered potentially suicidal and this always must be remembered in treating such cases

Treatment of Manic Depressive Psychosis and Involutional Melancholia Amphetamine sulfate in a total daily dosage of 10 to 30 mg may be effective in those patients in which there is only a mild depression Since the possibility of suicide is always present it is wise to refer the patient to a psychiatrist for treatment Prior to the use of convulsive shock therapy, patients with a severe depression, as the result of manic depressive psychosis or involutional melancholia required hospitalization for periods varying from months to years With the use of convulsive shock therapy the remission rate in the depressed phase of manic depressive psychosis is high The patient usually begins to show improvement within the first few weeks of treatment It has been estimated that about 80 per cent of the uncomplicated cases of involutional melancholia recover very rapidly after convulsive shock therapy There are two methods of producing therapeutic convulsions by the intravenous administration of metrazol and by the use of electroshock Electroshock therapy has almost completely replaced metrazol shock treatment because it is much easier to administer more exact, and less time consuming

Electroshock Therapy This form of treatment should be given only by a trained psychiatrist The treatment consists of producing a generalized convulsion by the application of a measured amount of electrical current for a fraction of a second The machine utilized in the treatment is attached to two electrodes fixed on each side of the patient s temples All possible precautions are taken to prevent injury to the patient during the induced convulsive seizure which usually lasts thirty to sixty seconds and of which the patient has *no* memory The number of treatments given usually depends upon the individual response of the patient and in the depressions an average of 6 to 12 treatments are given at the rate of 2 to 3 per week A longer

22. *Pain and Insomnia*

CARL C. PFEIFFER

Pain

PAIN RELIEVING and sleep producing agents are often confused with each other Pharmacologically they cause different actions and therapeutically they elicit different responses, although the control of one clinical problem may, indirectly permit control of the other If drugs are to be used judiciously they must be administered, if at all possible, for their specific effects There are times however when the drugs are used interchangeably with full appreciation of their pharmacologic properties clinically, the responses may be such as to warrant such use

ANALGESICS

Analgesics are drugs which alleviate pain but do not alter other modalities of sensation or disturb basic reflex patterns The most widely used analgesics are derivatives of salicylic acid either alone or in combination with other substances such as acetophenetidin, acetanilid and caffeine These preparations however, are of value only in alleviating certain mild or specific types of pain such as headache or the diffuse inflammatory pain of rheumatic fever Whether salicylate derivatives such as aspirin (acetylsalicylic acid) or its chemical congeners such as acetophenetidin actually raise the cutaneous pain threshold is equivocal The original studies utilized radiant heat applied to the forehead and were performed on only 3 subjects in a biased fashion Others workers have not been able to find a 35 per cent rise in the superficial pain threshold when aspirin is given under blind test conditions

Sonnenschein and Ivy have not found a significant elevation in the pain threshold of the tooth when 2 Gm of either aspirin acetophenetidin or acetanilid were given orally under completely unbiased conditions Thus the effectiveness of salicylates in relieving the pain of rheumatic fever must be ascribed to its anti inflammatory effect (demonstrated by Kapp and Coburn and now ascribed to either salicylate or its chemical congeners) On the other hand aspirin acetophenetidin acetanilid aminopyrine, and cinchophen undoubtedly are analgesic for headaches but this action must be ascribed to their ability to cause shifts in extracellular fluid and relative hydremia This will be discussed more fully under headache'

Derivatives of Opium

The most powerful type of pain killer *hitherto has been morphine and other de*

The patients with these toxic or symptomatic psychoses are usually confused, disoriented, apprehensive, and restless There may be disturbances of consciousness varying from slight clouding to complete delirium with illusions and hallucinations There are a variety of exogenous toxins such as alcohol, bromides barbiturates, opium, hyoscine, and many industrial poisons that can produce this syndrome * It is also seen in the presence of certain febrile diseases such as pneumonia and meningitis (less so now with the use of chemotherapy and antibiotics) and in some cases of uremia, hyperthyroidism, diabetes and cardiac failure

Treatment

This consists of removing or treating the underlying cause of the psychosis In the mediate symptomatic treatment sedatives st be used with caution particularly the biturate and bromides, for these drugs be the cause of the delirium Paralde and chloral hydrate are the safest s to use in controlling excited patients aldehyde is given in doses of 4–15 cc two or three times a day either by mouth or rectum When chloral hydrate is used it is given orally in doses of 1–2 Gm two or three times a day By using a nasal stomach tube an adequate dietary and fluid intake can be maintained in those patients who are unable or unwilling to take food or fluids by mouth Skillful nursing care will eliminate or minimize the ne mechanical restraints When some for restraint is necessary a restraining usually is tolerated fairly well by the tient Thiamine chloride in a dosage 50–100 mg hypodermically is given d in addition to the above measures in tients with delirium tremens

* See also Chapter 50

ORGANIC PSYCHOSES

This group comprises the psychoses tha result from structural damage to brain b vascular changes, senility, syphilis, tumors and degenerative diseases Confusion, defects in memory, comprehension, and judgment, personality changes, and emotional instability are the usual symptoms of these psychoses

Treatment

Dementia paralytica may be arrested, improved, or cured by the use of penicillin and/or malaria * When the symptoms are due to brain damage from brain tumor, the surgical removal of the tumor may result in the alleviation of the psychotic manifestations Cerebral arteriosclerosis and senility are the two major causes of the chronic organic psychoses and such patients account for about 25 per cent of the admissions to mental hospitals Treatment of these two conditions is limited to careful attention to general medical needs and custodial care

* See Chapter 39

patient in shock in whom a subcutaneous dose would not be absorbed because of the poor local blood supply, and all instances prior to an emergency operation The pre anesthetic depressant should be given intravenously to lessen the danger of emesis during the anesthesia and to provide the maximal degree of analgesia and narcosis prior to the induction of anesthesia

The potent analgesic drugs may be classified according to their degree of potency and their duration of action after a single subcutaneous dose (Table 22) Obviously, a drug such as morphine or methadone hydrochloride which has a long duration of action is more effective in alleviating the pain of cancer Battermann has pointed out that the patient with cancer is still hoping for a cure of his illness and thus if a drug gives pain relief for six hours the patient is pleased whereas two-hour relief with a short acting drug may be reported by these patients as ineffective In obstetric pain where moment to-moment control of respiratory depression is of paramount importance to prevent asphyxia neonatorum the parenteral use of a short acting analgesic such as heroin hydrochloride meperidine hydrochloride, demerol, or nisentyl every hour provides adequate analgesia In large doses meperidine is convulsant rather than depressant It will not completely obtund severe pain and will only be as effective as a large dose of codeine

Compounds such as the barbiturates and paraldehyde when used to relieve obstetric pain are not analgesic drugs but in sufficient and repeated doses produce amnesia so that the pain is not remembered There are many compounds used for the relief of specific pain without adequate evidence of an analgesic effect Thus the analgesic effect of counterirritants applied to the skin rests entirely on empiricism based on theories of referred pain One gram of procaine each hour given by intravenous drip will obtund certain types of pain such as causalgic states and the pain of severe burns The analgesic effect of this relatively nontoxic local anesthetic is now used extensively, after administration by the intravenous route

Certain drugs such as diopterin and teropterin have been advocated for pain relief in cancer patients although no data has been published regarding their analgesic action Due to the premature clinical use of these drugs a possible chemotherapeutic effect has been confused with an analgesic or euphoriant effect

Synthetic Substitutes

Recognizing the therapeutic limitations of morphine, pharmacologists and chemists have constantly sought more effective and less dangerous analgesics Efforts to alter the morphine molecule chemically have resulted in drugs that are either less effective or more potent but also more addicting i e, heroin and desomorphine

Metopon Metopon hydrochloride (" methyldihydromorphinone hydrochloride) may be a possible exception This compound is more effective orally and does not possess the extreme degree of addiction liability of desomorphine and heroin Its other actions are qualitatively the same as those of morphine differing only in degree Metopon has therefore been proposed and is being tested as an oral medicament for the treatment of patients suffering from the pain of cancer

Meperidine Because of extensive but misleading experiments with lower animals it was thought for several years that meperidine, (demerol isonipecaine pethidine) a relatively impotent synthetic analgesic, was indicated for pains associated with spasm of smooth muscle It is now known from the work of Gaensler *et al* that meperidine constricts the human biliary sphincters in a manner similar to that of morphine It is however probably

rivatives of opium Although morphine is extremely effective as an analgesic its undesirable side effects tend to counterbalance its efficacy in the relief of pain It produces emesis constipation respiratory depression tolerance to further injections, constriction of smooth muscles and occasionally severe pruritus However, its ability to cause potential addiction is its greatest drawback Thus, a neurotic or socially inadequate patient may desire morphine after experiencing the effect of a single dose and thus become addicted by further use A more stable individual will not show abstinence symptoms and physical dependence until injected with morphine four times per day for one or more weeks Addiction is most likely if the minimal dose no longer relieves the pain so that larger and larger doses must be given to get the same degree of relief (tolerance)

At the present time heroin and desomorphine are the most potent analgesics known However since these compounds are free from side effects they are invariably euphoriant and too addicting for widespread medical use

For severe pain the U S P dosage of morphine (10 mg) must be doubled and trebled to provide humanitarian pain relief This is in accord with the finding that in normal subjects a dose of 32 mg of morphine sulfate is required to raise the cutaneous pain threshold 100 per cent This same rise is obtained with 2–3 mg of dilaudid or 2 mg of heroin Thus the usual dose of dilaudid (2 mg) is much more apt in the author s experience to provide effective analgesia and should be used to obtund extreme pains such as occur in renal colic biliary colic coronary thrombosis dissecting aneurysm or in the pain of the acute abdomen Obviously, when operative intervention is the treatment of choice (or only treatment) the acuteness of the emergency should not be masked by an effective analgesic On the other hand dilaudid or morphine given slowly intravenously will provide sufficient reduction of reflex spasm in the acute abdomen for the surgeon to decide on the best operative site and make a more exact diagnosis Other indications for the slow intravenous injection of morphine or dilaudid are the

TABLE 22 CHANGE IN PAIN THRESHOLD AFTER ANALGESIC DRUGS

Drug	*Dose*	*Route*	*Maximum rise in pain threshold* (%)	*Duration of action* (Hr)
Morphine	30 mg	Subcutaneous	100	4–6
Dromoran	3–6 mg	Subcutaneous	100	6–12
Heroin	1 5 mg	Subcutaneous	110	1–2
Dilaudid	2 mg	Subcutaneous	110	2 4
Methadone	10 mg	Subcutaneous	100	6–12
Metopon	5 mg	Subcutaneous	100	4–6
Nisentyl	30 mg	Subcutaneous	50	1–2
Demerol (meperidine)	0 19 mg	Intramuscular	50	1–3
Codeine	60 mg	Subcutaneous	48	2–3
Ethyl alcohol	30 cc	Oral	40	1–2
Tetraethylammonium chloride	0 5 Gm	Intravenous	15	30–40 min
Paraldehyde	10 cc	Oral	20	2–3
Barbiturates*	Subanesth doses	Oral	0	
Quinine	0 5 Gm	Oral	0	
Caffeine	0 120 Gm	Oral	0	
Ergotamine	0 5 mg	Intramuscular	0	

* Beecher reports relief of clinically painful states with barbiturates.

muscle and thus may produce slightly less constipation but more nausea and vomiting

d,l Methadone is most valuable in the oral treatment of the pain of cancer If nausea and vomiting are encountered the patient may be given a single subcutaneous dose of 5 mg This inhibits the vomiting center for a long period and thereafter oral *d,l* methadone is better tolerated

TREATMENT OF PERIODIC AND COMMON HEADACHES

For the purpose of brevity specific head pains such as facial neuralgias, psychoneuroses (atypical pains), earache, and toothache, will be omitted from this discussion While these pains occur in the head, they are usually due to a determinable cause and are relieved by specific measures rather than by drug treatment Certain headaches accompanying such organic diseases as brain tumor and uremia will be included but not discussed, since in these instances the differential diagnosis is of paramount importance

Intracranial Pain Receptors

The only pain sensitive structures inside the cranial vault are the basilar portions of the dura mater, tentorium, falx cerebri, and the blood vessels The gray and white matter may be cut or cauterized without pain The skin of the head may be completely anesthetized with procaine, and headache can still be induced Ligation of the superficial arteries does not alter headache Pain is localized to the deep arterial walls and the supporting structures of the brain The afferent impulses are carried over the fifth nerve for the anterior and middle meningeal arteries

The posterior meningeal artery receives its nerve supply from the tenth and twelfth cranial nerves Alcohol injections indicate that the fibers of the first division of the trigeminal nerve are chiefly concerned with the mediation of headache Occasionally however, the sensory nerve roots as low as the second or third thoracic and all of the cervical sympathetic nerves have been severed in attempts to relieve intractable headache

Experimentally Produced Headaches

If 15 mg of glycerol trinitrate is rubbed on the skin, or 1–2 mg is applied sublingually, a headache that may last twenty four hours will result in certain individuals Tolerance is quickly established to this headache The acute headache occurs after the blood pressure has recovered from the marked drop produced by the nitrites

If 0 1 mg of histamine is injected intravenously into any individual a severe bilateral, throbbing headache will appear in about two to three minutes and will last about five minutes The headache does not occur during the drop in blood pressure accompanying the initial histamine shock but can be definitely correlated with a rise in blood pressure above the initial level If this is counteracted by continuous histamine infusion the headache is temporarily prevented Many physiologic procedures such as bilateral jugular compression which affect the cranial blood supply and raise the cerebrospinal fluid pressure will relieve the headache In histaminic cephalalgia (Horton s headache) a subcutaneous injection of histamine produces the syndrome

Many individuals will develop a headache if they do not obtain their morning cup of coffee Making use of this observation, experimental headaches may be produced by giving subjects increasing doses of caffeine Placebo capsules are then substituted on the fifth to seventh day of caffeine administration The subject will feel depressed in the morning and in the early afternoon a headache starts which reaches a maximum about 4 00 to 6 00 P M Nausea and vomiting may also occur with this type

atropine like in its action on the smooth muscle of the small and large intestine below the duodenum It provides relief of smooth muscle spasm in the asthmatic, when 25–50 mg given *slowly* intravenously may arrest the attack Since this is a chronic disease and meperidine is an addicting drug, care must be taken to choose stable patients in whom the addiction liability is low Morphine should almost never be used for the bronchial asthmatic for two reasons the patient may become addicted and the decrease in the cough reflex will decrease the elimination of mucus and so *the condition of the patient may be worse*

Meperidine is relatively safe for use in obstetric patients, but when given to ambulatory patients fleeting side actions such as dizziness nausea vomiting excitation buccal dryness, urticaria and euphoria may occur

Prolonged use of meperidine does not cause constipation as does morphine With doses ten times that of morphine a similar degree of analgesia can sometimes be obtained (although this does not equal 2 mg of dilaudid) Its duration of action (from two to three hours) is not as long as that of a comparable dose of morphine Primary drug addiction to meperidine has been seen frequently in asthmatics The main symptoms are marked tremor widely dilated pupils and occasionally convulsions The actual dosage taken per day by these addicts may be in gram quantities

Methadone During World War II German chemists synthesized a great number of compounds that possess marked analgesic properties The most outstanding of *these was d l methadone (d l 6 dimethylamino* 4 4 diphenyl 3 heptanone '10820 'amidone ' dolophine adanon) whose formula is shown in Fig 8

Following the war these compounds became available to American investigators As an analgesic *d l* methadone was found to be at least twice as potent as morphine and from twenty to twenty five times as potent as meperidine The pharmacologic properties of *d,l* methadone are similar to those of morphine in that it produces the characteristic Straub tail effect in mice excitation in the cat, and pupillary constriction in man and animals Its respiratory depressant effect is equal to that of morphine when equianalgesic doses are used The margin of safety is probably smaller than that of the opiates

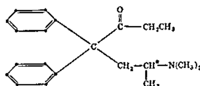


Fig 8 *d l* Methadone (*d l* 6-dimethylamino 4 4 diphenyl 3 heptanone 10820 amidone dolophine adanon)

The minimal effective dose of *d,l* methadone is 5 mg given subcutaneously Tolerance develops rapidly in animals In man the first five or six doses exhibit an increased effectiveness especially in sedative action Following the initial doses, tolerance to both the analgesic and sedative actions becomes manifest but less rapidly than is observed with morphine Some constipation and difficulty in urination have been observed but these tend to disappear as tolerance develops

d l Methadone has been substituted for morphine in the treatment of drug addicts with complete relief of the usual train of abstinence symptoms While it produces euphoria in most morphine addicts, this effect does not occur in the normal individual *Abstinence symptoms are slow to* appear after methadone withdrawal, but slight symptoms are manifest on the fifth to seventh day after the drug is discontinued *d,l* Methadone thus is used in the treatment of morphine addiction This drug has all of the side actions of morphine but is slightly less spasmogenic to smooth

10 *Toxic headache* may be due to carbon monoxide or lead poisoning and is similar to the frontal headache of fevers Other causes include *nitrite poisoning* and chronic tobacco poisoning

11 *Alcoholic hangover' headache* varies with each individual, but may be due in some instances to the marked changes in water balance that alcoholism induces

12 *Caffeine withdrawal headache* when induced experimentally can be relieved with caffeine amphetamine sulfate or oxygen therapy Probably this explains why many proprietary headache remedies contain caffeine

13 *Relaxation headache* is probably the cause of the Sunday headache in people of the business world Monday headache of the clergy, and day-off headache of the nurse It may be due to peripheral vasodilatation

Indefinite types of headache include

1 *Hunger headache* which is observed in individuals who abstain from food too long Such action results in headaches that may or may not be relieved by eventual food intake

2 *Excess starch or sugar headache* which is corrected by diet containing mainly the vegetables that grow above the ground

3 *Food allergy headache* which is most commonly caused by chocolate onions watermelon cabbage cucumber garlic green pepper peanuts and possibly milk

4 *Hypotensive headache* (orthostatic hypotensive syndrome) *fall in blood pressure* on standing accompanied by syncope and headache is characteristic Treatment is head up bed

5 *Mountain or altitude sickness* (as in aviators) is caused by acute lack of oxygen

6 *Headache due to unaccustomed exposure to a bright sun* may be a relaxation type of headache with peripheral vasodilatation

7 Headache occurs accompanying *epilepsy eclampsia, bleeding peptic ulcers Addison s asthenia, cerebral syphilis* and *myxedema*

Migraine

The mechanism of migraine is related to changes in peripheral vascular tone Lauter *Brunton suggested near the close of the* nineteenth century that the cerebral blood vessels must be involved in migraine headache inasmuch as he was able to obtain relief of his unilateral headache *by* carotid pressure Ray Graham and Wolff in 1937 demonstrated adequately that headache is associated with an increased excursion of the cerebral blood vessels *and that* when the headache is relieved by ergotamine tartrate the excursion of the blood vessels decreases

Theoretically an increased excursion of the cranial blood vessels could result from an increased arterial blood volume decreased blood volume increased blood pressure decreased blood pressure increased cerebrospinal fluid pressure and finally, a decreased cerebrospinal fluid pressure Most migraine headaches perhaps are accompanied by a decreased arterial blood volume with a relaxed peripheral vascular tone Therapy should hence be directed at increasing the peripheral vascular tone (ergotamine tartrate) or increasing the *blood volume (salt mixtures or hypertonic* intravenous solutions)

The therapy of acute migraine is varied The ascribed etiology and resultant therapy of *migraine* and most recurrent headaches depend on the specialist consulted The endocrinologist is likely to ascribe many cases of migraine to endocrine deficiency the allergist claims a high percentage of these cases when he diagnoses the condition the psychiatrist is likely to apply psychotherapy for all types of headache In most cases the interested general practitioner or neurologist achieves the best subdivision of the migraine syndrome so that

of headache It is possible to induce this headache in 60 to 70 per cent of normal individuals

If ' neo synephrin is given intramuscularly in doses of 8–10 mg a severe headache will occur when the blood pressure is elevated Ephedrine also will produce headache in overdosage These headaches are perhaps comparable to hypertensive headaches

The mechanism of headache due to carbon monoxide has been studied extensively by Swedish scientists and by Von Oettingen at the National Institutes of Health A rise in pressure of the cerebrospinal fluid has characteristically accompanied the headache and it appears that this is the only experimental headache which shows this phenomenon

In subjects who are susceptible it is possible to reproduce a relaxation headache consistently by having them follow a daily cycle of increased activity and decreasing sleep The headache is then precipitated by having them sleep late This may explain the characteristic Sunday headache of the business executive or the postexamination headache of the student

Schumacher has found that in many patients undergoing fever therapy the headache is accompanied by an increased excursion of the cerebral blood vessels Many febrile diseases may be accompanied by severe frontal headache as their initial symptom of these the typhus group (rickettsial type) is the most important

Differential Diagnosis

Headaches may be grouped according to the cause into certain definite types

1 *Eyestrain headache* is frequently occipital or even nuchal It is relieved by adequate correction or rest

2 *Empyema of the nasal sinus* often accompanies a cold It usually requires roentgen ray diagnosis Migraine and histamine cephalalgia are frequently accompanied by a nasal discharge, which may confuse the diagnosis

3 *Brain tumor* is accompanied by morning headache (frontal or generalized) which is intensified by change of posture Sitting up in bed in the morning may cause projectile vomiting

4 *Post spinal puncture headache* follows decreased pressure of the cerebrospinal fluid Pickering has shown that the cerebrospinal fluid pressure may be abnormally low for days following lumbar puncture Assuming the horizontal position is the best treatment The headache does not respond to gynergen but oxygen may help

5 *Hypertensive headache* is worse in the morning and disappears by noon ('bursting headache) Treatment with a head up bed may be effective

6 *Migraine headache* occurs twice as frequently in the female as in the male and may be familial It may be unilateral, scotomatous, periodic, and accompanied by nausea and vomiting The onset often is at puberty with relief at the menopause, at which time frequently hypertension develops It is relieved by pregnancy, occurs frequently with the menstrual period, occurs periodically with relaxation and frequently is preceded by diuresis

7 *Histamine cephalalgia* occurs from age 30 to 40 years Onset is sudden and so is relief There is unilateral lacrimation and rhinitis, and local vasodilatation It apparently is produced by histamine and relieved by raising the tolerance to histamine or by the use of antihistamine drugs

8 *Posttraumatic headache* results from trauma associated with head injury without rest The patient should stay in bed with the head up or down

9 *Psychoneurotic headache* occurs in patients who complain of a pulling sensation, a headache on top of head or a tight band around head Headaches frequently are associated with schizophrenia

Histamine infusion to raise tolerance Since histamine is a pure chemical, patients are not desensitized to histamine but do have their tolerance to its pharmacodynamic effects raised While this is used extensively as a 1 250 000 solution there have been *no controlled studies on its effectiveness*

Ammonium chloride for the prevention of migraine associated with menstruation The drug is started ten days prior to menstruation and progesterone and estrogen therapy begun three or four days before the onset of the menses

Phenobarbital or *bromides* which in sedative doses may be effective in those patients whose attacks occur when they become *unduly excited* Because of the danger of bromism the use of bromides should be by individual nonrefillable prescriptions

Relief of Clinical Pain

TABLE 23 summarizes the representative pain relieving treatments for a variety of clinical conditions The relief of clinical pain does not depend on the indiscriminate use of analgesic drugs Pain may be due to *many causes and its relief should always be* effected by the most suitable physiologic procedure before resorting to the use of potent analgesics The list is not intended to be complete but to indicate the need for individual consideration of the cause of pain and the treatment of the underly*ing condition or perhaps the symptomatic* relief of the pain

Sleep-producing Drugs

THE use of *sleep producing* drugs (hypnotics) has greatly increased in the United States This can be ascribed in part to our Stop and Go living which like our Stop and Go driving is exceedingly hard on the mechanism The busy executive and even the average city dweller desire to turn consciousness on and off Amphetamine may be used in the morning to establish staccato efficiency and alcohol or barbiturates may be used at night to smother any still *smoldering nervous activities* Thus con*tinually goaded with drugs the body* frequently may need rest cures which decrease tolerance to drugs

The physician should make a serious *effort to ascertain the cause of insomnia* and prescribe for the basic cause Occasionally simply the use of a black felt binder over the eyes may induce sound sleep in those who must sleep in the daytime Ear plugs will decrease extraneous noise Most important as a hidden cause of insomnia may be the possibility of conflicts or emotional turmoil

For those patients who are in need of sleep producing drugs and cannot employ barbiturate therapy the use of chloral hy*drate in a liquid prescription* or emulsion of paraldehyde can be recommended The *following prescription* for chloral hydrate is reasonably palatable

the patient obtains the proper therapy for his particular case

Ergotamine tartrate and dihydroergotamine ("DHE 45") are effective remedies If given at the onset of an attack either 0 3 cc intravenously or 0 5–1 0 cc. of 1 2000 'gynergen' intramuscularly will result in relief in one to two hours in 90 per cent of the patients (Twice this dosage should be used if "DHE 45' is employed) Atropine 0 5 mg may decrease nausea and vomiting produced by 'gynergen and 10 cc of 10 per cent solution of calcium gluconate given intravenously may relieve the muscle cramps produced by 'gynergen If oral treatment (which is not nearly as effective) is attempted, the 1 mg tablets should be placed under the tongue until completely dissolved This may be repeated up to five times in a single twenty four–hour period without danger of poisoning If 2 5–10 mg of amphetamine ('benzedrine') sulfate or 0 1 Gm of caffeine (Horton) is combined with the oral dose, more effective relief is obtained possibly because of synergistic action in augmenting the peripheral vasoconstricting action

A common analgesic prescription of the proprietary type is

	Gm or cc
Acetophenetidin	2 0
Acetyl salicyclic acid	4 0
Caffeine citrate	1.2
Codeine phosphate*	0 8

Mix and put in capsules #24
Label Take one or two capsules at first sign of headache

* May be added depending on severity of attacks

Pure oxygen (6–8 liters per minute flowing through a Boothby or nasal mask) may abort an acute attack if it is used

Carbon dioxide CO_2 (5–10 per cent) and oxygen (90–95 per cent) may abort an attack The patient inhales 5–10 per cent carbon dioxide in oxygen to the point of marked discomfort (usually four to five minutes) This should be repeated several times for maximal therapeutic effect

Some migraine patients obtain marked relief from their syndrome after the use of *antihistamine* substances such as diphenhydramine (benadryl) and tripelennamine ('pyribenzamine') A few can be relieved by parenteral papaverine therapy (60 mg intravenously)

Sodium nicotinate may relieve the migraine syndrome in selected cases

From 0 1 to 0 2 Gm of 'octin,' given subcutaneously, is also credited with relief of the acute migraine syndrome

The short acting *barbiturates,* such as pentobarbital may be effective in producing sleep in spite of the migraine syndrome, and the patient may be free of the attack when he awakens

Supportive therapy to prevent migraine attacks includes the use of

Thyroid as even when a normal basal metabolism rate exists a migraine patient is relieved frequently by thyroid therapy Adequate tests must be made from time to time to avoid thyroid overdosage

Calcium gluconate or *lactate* (12 cc. daily) which is particularly useful in patients who show a decreased serum calcium and elevated serum phosphorus

A *calcium lactate and potassium chloride* mixture which provides the same proportion of these ions as is present in the blood serum may be given based on the theory that this proportion is necessary to increase the arterial blood volume The mixture is taken in 0 7 Gm doses three times daily after meals It consists of a ratio of 308 Gm of calcium lactate to 225 Gm of potassium chloride Sixty per cent success in treatment of migraine headache has been reported with this mixture While it is more effective as supportive treatment, it also may be used to treat acute attacks Aspirin and calcium potassium should be taken when diuresis is first noted

Diet restriction, the best dietary treatment having been found empirically to consist of a low carbohydrate diet.

largest margin of safety of any of the sleep-producing drugs and thus is especially suited to the treatment of maniacal states Unfortunately, paraldehyde is not sufficiently soluble in water to permit its being prescribed in diluted form Furthermore, paraldehyde congeals at 10° C so that if cooled by ice chips the paraldehyde coats the ice and is not ingested

Suspensions of paraldehyde (40 per cent) in water or licorice syrup may be made with 2 per cent powdered gum tragacanth or by using a saturated aqueous solution of lecithin This may be prescribed as follows

	Gm or cc
Paraldehyde	40
Powdered gum tragacanth	2
Syrup of licorice to make	100

Label One teaspoonful in water at bedtime

	Gm or cc
Paraldehyde	40
Saturated Solution of lecithin to make	100

Label One teaspoonful in water at bedtime

These suspensions do not irritate mucous membranes and may be used either orally or rectally When ingested the diluted suspension produces a menthol like sensation Dr F A Gibbs has found the rectal use of this suspension to be excellent for producing sleep in infants and undoubtedly those who use paraldehyde rectally for obtunding labor pains will find it to be better tolerated than raw or diluted paraldehyde

In both of these prescriptions the dose of sleep-producing drugs has been kept below that which will produce death if the entire prescription is taken at once with suicidal intent This rule applies most emphatically to barbiturate prescriptions since one third of all suicidal deaths are now aided or accomplished by the barbiturates Thus short acting barbiturates should be prescribed in lots of six to twelve capsules at a single time In those states which do not have laws against the refilling of barbiturate prescriptions the physician should write N R (non repetatur) on the prescription so that refill is impossible If the patient cannot see his physician regularly he may be given several postdated prescriptions clearly labeled *not to be filled* before the inscribed date

Barbiturates

Barbituric acid derivatives can be used to produce sedation (phenobarbital) to induce sleep (seconal amytal pentobarbital) to depress the motor cortex and thus act as an anticonvulsant (phenobarbital), and to give partial or complete surgical anesthesia (pentothal) The mechanism of their depressant action on the cortex is believed to represent an interference with the enzyme systems which are essential for the metabolism of carbohydrates An alternate theory suggests that barbiturates are agents that affect the central nervous system by blocking an essential stimulant metabolite

Of the hundreds of barbiturates which have been synthesized only a few have been found suitable clinically for their hypnotic and sedative action Only three of these are listed in the United States Pharmacopeia (barbital phenobarbital and pentobarbital) the remainder are found in New and Non official Remedies The various barbiturates differ mainly in their time of onset duration of depressant action and in their suitability for use as intravenous anesthetics

The acid form of these drugs is stable alcohol soluble and insoluble in water while the alkali salts of these drugs are water soluble but deteriorate rapidly in solution For oral use either the acid form or the sodium salt may be used with equal effect

Duration of Action The barbiturates are classified on the basis of their duration of action in the body If a barbiturate depresses for longer than six to eight hours

	Gm or cc
Chloral Hydrate syrup	10
Peppermint water to make	60

Make a solution

Label One teaspoonful in a glass of water just before retiring

Paraldehyde may be used in hospitalized patients to produce sleep but is objectionable in the ambulatory patient because of the characteristic odor imparted to the breath However, paraldehyde has the

TABLE 23 TREATMENT OF CLINICAL PAIN

Painful states	*Recommended treatments*
Abscess, acute boils etc	Incision and drainage Penicillin, sulfonamides, moist heat
Angina pectoris	Glycerol trinitrate, amyl nitrite
Biliary colic	Nitroglycerin, amyl nitrite, aminophylline, "dilaudid"
Burns, severe	Pressure bandage, "dilaudid," morphine, methadone, intravenous procaine
Cancer cells, invading	Testosterone, diethylstilbesterol, specific cellular antimetabolites such as nitrogen mustard, methadone, metopon, morphine, "dromoran"
Causalgia	Sympathetic block or "trigger-point" block with procaine, tetraethylammonium chloride intravenously, continuous tetracaine spinal anesthesia
Central (thalamic) pain	No effective treatment, methadone, frontal lobotomy?
Claudication	Rest, sympathectomy, physical therapy
Dysmenorrhea	Atropine, ephedrine, amphetamine, "pavatrine," "trasentine," antihistamine drugs, acetylsalicylic acid, acetophenetidin, codeine, phenobarbital
Glaucoma	Physostigmine, pilocarpine, di isopropyl fluorphosphate, operative relief of tension
Gout	Acetylsalicylic acid, colchicum, cinchophen, ACTH, cortisone
Headache	Acetylsalicylic acid, caffeine, acetophenetidin, ergotamine tartrate, oxygen therapy (+5% CO_2?), sodium nicotinate, antihistamine drugs, codeine
Heat cramps	Salt tablets
Hematoma under finger nail	Trephine nail with sharp point of a sterile scalpel or pen knife
Hemorrhoidal pain	Hot baths, topical anesthetics
Itch	Antihistamine drugs, menthol-phenol paste, calamine lotion, intravenous procaine
Myalgia	Procaine block, counter irritants, physical therapy, d tubocurarine in oil, oral "myanesin"
Night cramps of voluntary muscle	Quinine 0 3 Gm. at bedtime, calcium lactate 1 Gm three time a day
Obstetrical pain	Heroin, meperidine, nitrous oxide, "nisentyl" (paraldehyde, scopolamine, or barbiturates will produce amnesia)
Otitis media	Phenol or antipyrine locally, penicillin, sulfonamides
Paraplegic pain	Anterolateral cordotomy
Peptic ulcer	"Dibutoline," atropine, antacids
Phlebitis	Physical therapy, sympathetic block
Pleurisy	Partial pneumothorax, codeine to control cough
Postherpetic pain	Pituitary extract, physical and radiation therapy, procaine or alcohol block
Postoperative gas pains	Duodenal and rectal tubes neostigmine, pituitary extract
Psychogenic pain	Phenobarbital, psychotherapy
Renal colic	Meperidine, nitroglycerine, aminophylline, "dilaudid"
Rheumatism	Salicylates, acetylsalicylic acid acetophenetidin
Sprain of joint (ankle, etc)	Infiltrate with 2% procaine hydrochloride (without epinephrine), physical support
Trigeminal neuralgia	Trichloroethylene, procaine and alcohol blocks

ment stage of anesthesia and become uncontrollable

Anesthesia The barbiturates fall short of meeting the requirements for an ideal anesthetic in two major aspects First they are poor analgesics second, the large doses required for anesthesia cause a decrease in the margin of safety except in the case of the ultra short actor thiopental sodium *which allows a fairly accurate moment-to-moment control owing to the rapid recovery after termination of injection provided it is used for a short operation* When used for several hours moment to moment control may be lost owing to accumulation of thiopental and a slower rate of degradation

All of the barbiturates except the long actors are destroyed in the liver and apparently the ultra short thiobarbiturates also are destroyed in the blood stream and kidney The long actors barbital and phenobarbital are eliminated to some extent in the urine However with massive doses small quantities of the other barbiturates may spill over into the urine, thus indicating a high renal threshold for all but the long actors

Treatment of Barbiturate Poisoning These drugs are often taken unintentionally in large doses and chronic poisoning occurs The patient may fail to develop a deep sleep and mechanically may continue to take the remainder of the tablets in the bottle This condition of 'automatism may result in accidental death The signs and symptoms of barbiturate poisoning are deep coma small fixed pupils, corneal anesthesia low blood pressure, shallow respiration, and a fast, weak pulse Specific treatment is as follows (1) administer gastric lavage with activated charcoal suspended in water, and allow 30–60 Gm of sodium phosphate or sodium sulfate to remain in the stomach (2) maintain adequate respiratory exchange with oxygen therapy and assist respiration if needed (3) give 2 L isotonic sodium chloride hypodermically and 100–200 cc of a 10 per cent glucose solution intravenously to act as diuretic agents (4) administer 1 mg per minute of a *1 1000 picrotoxin solution until* consciousness is resumed or until the limit of tolerance (twitching of facial muscles) is reached or 20–60 mg of amphetamine intravenously every thirty minutes (5) maintain body temperature (6) change the position of the patient every three or four hours

Osgood of the Milwaukee Sanitarium has reported convulsive seizures after withdrawal of barbiturates in patients who had taken sufficiently large amounts of the short acting barbiturates to become tolerant to their depressant effects This phenomenon has also been observed by others in psychoneurotic patients who have consumed increasing dosages None of these patients had ever had epilepsy In view of these marked abstinence symptoms and the frequency with which suicide is attempted with barbiturates either greater care *in prescribing or more stringent* control of the barbiturates is needed Since laws are still ineffective a thorough educational program is needed

TABLE 24 BARBITURATE HYPNOTICS

Action	Drug	Hypnotic dose (Gm)	Duration (Hr)
Long	Phenobarbital (U S P) (luminal)	0 015–0 20	24+
Long	Barbital (U S P) (veronal)	0 3 –0 6	12 24
Intermediate	dial	0 1 –0 3	6 10
Intermediate	neonal'	0 05 –0 10	6–10
Short	amytal	0 1 –0 3	4–8
Short	Pentobarbital (U S P)	0 1 –0 2	4–6
Short	seconal	0 1 –0 3	3–6
Ultrashort	Thiopental sodium (intravenous use)		¼–2

the patient will still be dizzy on awakening and thus will have a 'hangover from the hypnotic Shorter acting barbiturates have been sought, since these act rapidly and if sleep is quickly induced the patient usually will remain asleep Examples of the different actions of barbiturates are seen in Table 24

Nature of Action The barbiturates have an effective sedative and hypnotic action For this reason they are used to a great extent in simple insomnia, hysteria hyperthyroidism and certain nervous disorders These drugs have a maximum hypnotic action combined with a minimum local irritant effect on the gastric mucosa and for this reason they may be dangerous if used promiscuously (One solution that has been proposed for the barbiturate menace is to combine 15 mg ipecac with each capsule to cause emesis when overdosage occurs) Under proper conditions sleep can be induced within a half hour after the oral administration of a small dose However in the presence of severe pain repeated administration of barbiturates may cause delirium In this respect the analgesic properties of the barbiturates differ markedly from those of the morphine derivatives and the salicylates The latter drugs will produce analgesia without necessarily producing sleep or unconsciousness, while the barbiturates will not produce analgesia until the first stage of anesthesia has been reached

If a patient is unable to go to sleep but sleeps well once he is asleep the short acting barbiturates should be administered In instances when the patient is unable to remain asleep for any length of time, an intermediate or long acting drug should be administered Barbiturate induced sleep usually results in a refreshed awakening but in rare cases nausea, vertigo, and headache may appear after awakening

It should be remembered that the duration of sleep and the aftereffects produced depend not only on the barbituric acid derivative used and its route of administration but also on the slight physiologic and pathologic differences which exist among individuals The barbiturates can be used to augment the analgesic drugs, such as acetylsalicylic acid (aspirin) aminopyrine and acetophenetidin This use probably depends entirely on sedative action

The longer acting barbiturates are used to produce sedation and should be administered in small frequent doses Barbiturates are used as preanesthetic depressants and for the prevention of stimulant reactions from the local anesthetics To prevent reactions from local anesthetics short actors may be used immediately before the operation or the long actors may be used the night before Some obstetricians use short acting barbiturates during the early stages of labor This produces amnesia, but occasionally patients will enter the excite

in the second World War recognized that the emotions can make people as sick as can bullets and germs Physicians returned from military service determined to learn more about the relation of the emotions and ill health They subscribed to the notion that the term *psychosomatic* must be un hyphenated, that it must mean the relation of psyche to soma as well as the reverse and that it is properly the scientific application of both physiologic and psychologic technics to the study of the sick human being in an effort to make a definitive diagnosis in preparation for comprehensive medical care

There remains some question as to whether the term should be used to designate an ailment although it is used in that way by many workers who refer to certain diseases of the vegetative nervous system such as migraine or asthma as psychosomatic disorders If the term is used in this way it means that the disorder is one that can be understood only when emotional factors are studied as well as physical factors If not used in that sense the term refers to a technic an approach that applies equally to all aspects of medicine and surgery a methodology It is an interim term good for the present time to be abolished when all medicine becomes psychosomatic medicine That day is fast approaching

PSYCHOSOMATIC DIAGNOSIS

In the traditional medical curriculum the psyche has been placed last The patient has been studied by means of the bare facts of medical history, usually organically slanted by a thorough physical examination and by the various laboratory ' work ups If all are negative then and then only the diagnosis of functional or psychogenic disorder has been made

There are grievous errors involved in this kind of thinking Diagnosis by exclusion results in the patient accumulating a thick sheaf of documents containing the results of hundreds of dollars worth of laboratory procedures becoming fixed in his neurotic obsession with the disorder and being often subjected to many medical and surgical procedures in an effort to achieve a cure In addition to this physiologic investigation an effort must be made to build up certain postulates from positive personality data in an effort to establish a diagnosis of neurotic or psychosomatic illness a condition which has its own distinctive features, discoverable by personality study The details of the diagnostic survey of the patient s personality and emotional history are, of course beyond the scope of this discussion but are readily available in many texts

If this study of the personality is added to the physical and physiologic studies definitive diagnosis should be possible In other words just as ' physical medicine teaches that an etiologic anatomic and physiologic diagnosis must be made so does psychologic medicine teach that a clinical a dynamic and a genetic diagnosis must be obtained The dynamic diagnosis refers to the emotionally disturbing event in the cross-sectional history that has precipitated the illness the genetic diagnosis refers to the longitudinal section of the life history which establishes the background for this emotionally disturbing event Having established a diagnosis the controversial question of treatment arises

PSYCHOTHERAPY

How far should the general practitioner go in dealing with these problems? How much of the diagnosis and the treatment lies within his province? Should he ignore the psyche in dealing with his patients referring them to psychiatrists as soon as he suspects that the emotions are playing a part? This is intimately bound up with the question What is psychotherapy?

Psychotherapy is something more than

23. Psychosomatic Principles in Treatment

EDWARD WEISS

PSYCHOSOMATIC is a relatively new term but it describes an approach to medicine as old as the art of healing itself It is not a specialty but rather a point of view which applies to all aspects of medicine and surgery It does not mean to study the soma less it only means to study the psyche more It is reaffirmation of the ancient principle that the mind and the body are one that they function as interactive and interdependent organs — a principle which has always guided the intelligent general practitioner As a science psychosomatic medicine aims at discovering the precise nature of the relationship of the emotions and bodily functions Research on the subject is founded on the confluence of modern physiologic investigation as developed by laboratory science and animal experimentation and of the discoveries of psychoanalysis both representing dynamic outgrowths of medical practice

Physicians have always known that the emotional life had something to do with illness but the structural concepts introduced by Virchow led to the separation of illness from the psyche of man and a consideration of disease as only a disorder of organs and cells With this separation of diseases into many different ailments came the development of specialists to attend to all of these distinct diseases With the specialists came the introduction of instruments of precision and the mechanization of medicine began Medicine now became the study of the organism as a physiologic mechanism because of the impressiveness of blood chemistry electrocardiography and other methods of investigation Study of the psychologic background of the patient because it was not considered as scientific as laboratory work ups was often held in contempt and largely ignored This period may be referred to as the machine age in medicine Remarkable developments have occurred during this period of laboratory ascendancy but it must be admitted that the emotional side of illness has been almost entirely neglected

MEANING OF THE TERM PSYCHOSOMATIC

The second World War did a great deal to change this state of affairs and this new interest in psychiatry stems largely from the impetus given by military experience because almost every physician who served

swallow this or that environmental situation, he cannot *stomach* this or that thing that has happened to him Atypical neuralgia of the arm or face may represent the response to focal conflict rather than to focal infection For example, the pain may represent the response to two opposing forces within the individual—because he would like to strike someone but is prevented from doing so by the affection and respect that is mingled with his hostility, he gets a pain—atypical neuralgia

Throughout the body one can often find a homely explanation which explains the otherwise mystifying complaints either in whole or in part—the physical expressions of tension—and provides a ready avenue for the patient to talk about some of the problems which are disturbing him Patients often are seen with shortness of breath or sighing respirations which, so to speak, represent a load on the chest they would like to get rid of by talking about some of their problems Patients with weakness in the legs, shakiness, and tremors but without organic disease, may be made to understand that the complaints represent physical evidences of *insecurity,* a relation which can usually be ascertained by the physician talking to the patient about his feelings of inadequacy This is a very useful approach in minor psychotherapy It offers explanation in simple terms to the patient who at times cannot understand how the mind may rule the body

Anxiety Anxiety is the nucleus of disorders of this kind and it often finds a physical expression The patient rationalizes that physical expression in some phobia which unfortunately is often added to by his medical advisor Most women suffer from the fear of cancer even though they may not admit it Many men do too When examining a patient who presents a vague complaint an ache, or discomfort, fatigue or a swelling which she thinks she sees, and the physician is sure she is free from organic disease, he will do well to reassure her as to the absence of cancer Significantly, in the last few minutes as the patient is leaving she may say, I am so glad to know that you find me all right, doctor I was so afraid I was developing cancer'

Another expression of anxiety is the fear of *heart disease* in which the iatrogenic influence is often seen A patient develops an anxiety attack in a crowded room, suddenly feels faint and breaks into a sweat, the heart races, the pulse pounds and a doctor is called He feels the pulse, listens to the heart gravely or overlong takes the blood pressure, then says to the patient, I don t *think* there is anything the matter with your heart, but you better take it easy, or Your heart *seems* to be all right but you had better take these drops for a while

Here may be the beginning of a cardiac neurosis The heart has always been known as the seat of the emotions just as the stomach is a sounding board of the emotions People fear heart disease and physicians have to be on the alert not to add to their apprehensions Too often patients are seen with organic heart disease in whom the disability is caused not by the heart but by concern and preoccupation with the heart Cardiac neurosis is a very common disorder and generally recognized as emotional in origin and approachable only by psychotherapy

But many symptoms in organic heart disease are brought about by psychic stress and the disability might be indefinitely postponed if that psychic stress could be dealt with adequately Many cardiac patients come to grief long before their time because they have not been treated satisfactorily from an emotional standpoint The emotions add a real burden to the work of the heart, not only in stress and strain but also in disturbed function

A third common rationalization of the patient's anxiety is the fear that he is *losing*

the art of medicine as practiced by the old family doctor—reassurance in large doses, a kindly, sympathetic manner, perhaps sending the patient away on a vacation It s a medical discipline, perhaps not as recise as the exclusively physical biologic ences, but nevertheless a system which can be taught, that has rules of order, and that can be learned if we start soon enough in our medical curriculum

Minor Psychotherapy

There is a minor psychotherapy as well as a major psychotherapy, just as there is a minor surgery and a major surgery Most physicians are prepared and competent to perform this minor surgery However physicians recognize the indications for major surgery and send the patient to a surgeon for further help Their responsibility in regard to psychotherapy in general medicine is the same The great majority of patients whom they see, particularly with chronic illness, have an emotional component to their illness that has entered to some extent into the problem of their ill health Most of these emotional components can be treated by the general practitioner

Patients with chronic illness may be classified into three groups One-third have an illness that cannot be accounted for on the basis of physical disease, and in which emotional factors are chiefly responsible another third have organic findings, but these findings do not explain the entire illness in other words the symptoms are out of proportion to the disease In the final third the physical factors seem entirely responsible for the clinical picture the patient resents If these estimates are accurate—nd studies from many sources confirm iem—it stands to reason that an important sk in medicine cannot be ignored Every ie who deals with sick human beings has deal with the psyche, no matter how insily or how unconsciously he does it e point is that it must be done with understanding and that the technics be taught and practiced as minor psy therapy in general medicine

Indeed, the physician cannot afford to practice psychotherapy In a study "thick-chart patients," when the expense the various laboratory procedures and visi to successive medical addresses are balance against an hour or two spent in trying to understand the patient as a human being it becomes apparent that the psychosomatic approach is less costly to both patient and physician in time and effort, besides averting harmful procedures That does not mean, of course, that the man who practices general medicine has to sit down and spend an hour with every patient, because the great majority of patients suffer from minor or acute ailments easily understood without a prolonged discussion of emotional factors But for chronic illnesses frequently subjected to unnecessary medical and surgical treatment, the physician has to take time, and he saves dollars and cents as well as human resources when he does so

Problems of Minor Psychotherapy

Numbers of patients present themselves with that central core of psychosomatic disturbance anxiety—anxiety which grows out of emotional conflict It does not do much good to ask a patient if he is worried about anything because the things that disturb him are not often in his consciousness They express themselves as bodily disturbances for the very reason that they are repressed, pushed out of consciousness thereby creating tension or pressure from within

Organ Language Often such tension will be expressed in symbolic language, a kind of body or "organ language" For example the individual who cannot eat, who cannot tolerate food, who is nauseated or vomits, often cannot tolerate something in his environment Thus, he cannot

evaluation of the individual's wish to get well or the reverse, the unconscious desire to remain sick So often the patient repeats over and over again that he is eager to get well but the unconscious forces working to perpetuate the illness are recognizable In fact the more the patient complains the more it may be suspected that his unconscious wish to *remain sick is the force which will exert itself*

Gain from Illness

The amount of emotional satisfaction permitted by the illness—in other words what the patient gains from the illness—is a matter of great importance in assessing the capacity for recovery Sometimes illness is the best answer to the problem Patients who have lived the better part of their lives, especially when a realization of their shortcomings in relation to a marital or business problem might prove disastrous had better not be disturbed by efforts to show a relationship between symptoms and life situation Not only the intellectual ability but also the emotional capacity of the patient to face himself must be assessed

Transference

Transference reactions which have to do with physician patient relationships are important in evaluating chances for recovery The physician must also be suspicious of people who outwardly seem affable and agreeable and apparently eager to cooperate but who inwardly are suspicious and *skeptical and actually refuse to cooperate*

Fear of Disease

A rough estimate which every physician is in a position to make daily is the degree of obsession regarding a fear such as that of cancer Many patients present a fear of cancer as *the first layer of their anxiety* If they have a high degree of maladjustment the fear will quickly return or be replaced by another fear

Age

One of the most important criteria for recovery is the age of the patient and the length of time that his illness has lasted If a middle aged person has been a semiinvalid for emotional reasons for many years one is less hopeful about the chances of recovery than in a young person with an *illness of relatively recent origin* Young people of course are more malleable than old

Origin of Disorder

Another estimate of value is the strength of the precipitating force If an illness appears *for a relatively trivial* reason and then maintains itself, the prognosis is apt to be more serious than in an illness which appears only under great stress and then lessens as the individual makes some spontaneous recovery If the individual was relatively well adjusted and then met an extraordinary situation as many of the men in military service did he might break down but recover on return to normal conditions *On the other hand* a sensitive individual with a marked neurotic pattern to his personality may break down with psychosomatic illness for seemingly trivial reasons

Intelligence

One often hears patients say, 'But doctor, I ought to be intelligent enough to handle this problem Unfortunately it is not so much a matter of intelligence as of feelings The will and the intellect are really weak instruments compared to the emotions The intellect has very little to do with these problems therefore although it is a tool which must be used in understanding and helping these patients it is not a matter of first consideration in judging their capacity to recover One need not be gifted intellectually in order for psychotherapy to be successful Of course a sub

his mind He complains that his memory is slipping, that he cannot concentrate, that he is so preoccupied he cannot read—he must read over and over to understand What he does not say is, 'I m afraid I am losing my mind With it often goes the thought of suicide He may be helped greatly by being allowed to share his burdens of anxiety and by being told that his problem is emotional not mental

These problems in minor psychotherapy can be dealt with and if the neurotic predisposition is not too great the patient can be helped immensely when these physical manifestations of anxiety are treated

One might summarize minor psychotherapy in these points

1 Give the patient time to tell his story listen rather than talk
2 Get to know the patient as a person rather than just as a medical case look for the person in the patient
3 Make the physical examination (including laboratory studies) as complete as necessary Exclude or evaluate physical disease
4 Reassure the patient that there is no evidence of cancer, heart disease, or mental disease
5 Explain to the patient that he has a disorder and not a disease (i e irritable colon not colitis) that symptoms are real (not imaginary) and although unpleasant will do no damage to the body
6 If disease is present, explain that symptoms are out of proportion to the disease (for example, the headache and fatigue in hypertension)
7 Look for and explain the time relationship between onset of illness and emotionally disturbing events
8 Encourage discussion of personal problems family setting marital situation work social life
9 Ask the patient to give his own explanation of his illness and re-educate him on the mechanism of symptom formation how tension of emotional origin causes symptoms
10 Instead of cautioning rest, urge the patient to engage in more work and social endeavor 'Carry on in spite of symptoms This externalizes psychic energy (libido) and diverts attention from body sensation
11 If drugs are used, explain their action avoid 'mystery'
12 Try to desensitize, by repeated discussion, against noxious environmental influences unfriendly relatives, critical employers etc If desensitization is not successful and modification of environment is impossible, then a change of environment is indicated

Forces Which Favor Psychotherapy

In some cases it is difficult for the patient to appreciate the necessity of visiting a physician when he does not get a prescription, an injection, physiotherapy, or an operation To "just talk about himself' does not seem worth the effort, the time, or the money There are certain forces, however, which favor psychotherapy The first is the distress which the patient has been suffering and which has been unrelieved by traditional medical or surgical attention The second is the standing and prestige of the physician who tells him that he needs psychotherapy The third may be the family, who may have a greater belief in the efficiency of psychotherapy than the patient, or who may be tired of putting up with the patient s long drawn-out illness or distressing eccentricities It must be admitted that the resistance to psychotherapy causes many patients to make trials in every other direction and to suffer considerably before they will accept a treatment which calls for a scrutiny of their emotions and their relations to other human beings

Prognosis

The capacity for psychotherapy can often be judged on the basis of the material discussed, but one must also attempt an

24. Allergy

SAMUEL M FEINBERG

THE therapy discussed in this chapter will be concerned primarily with the atopic manifestations such as asthma allergic rhinitis eczema and urticaria Atopy is the class of allergy characterized by hereditary tendency immediate whealing skin reactions and the presence of transferable sensitizing antibodies (reagins)

Objectives of Treatment

THE present concept of the mechanism of production of allergic manifestations particularly atopic is as follows The allergic person by previous sensitization to a particular antigen (such as ragweed pollen) develops antibodies (reagins) which become attached to tissue cells (in the nose for example) Perhaps because of interlocking configurations the antigen on re exposure is able to unite with its specific reagin This union results in the liberation and activation of histamine from the cell The liberated histamine produces characteristic pharmacologic effects on the sensitized and adjacent cells The effects elicited are increased capillary permeability vasodilatation and stimulation of involuntary muscle and mucous glands In this way are produced the localized edemas such as are found in urticaria hay fever edema of bronchial mucosa in asthma and perhaps allergic headache The effect of this histamine on smooth muscle is apparent in the bronchospasm of asthma the colicky pain of intestinal allergy the pylorospasm of gastric allergy and the urinary frequency in bladder allergy Alteration in secretion of mucous glands is exemplified in the production of typical tenacious sputum in asthma and the mucus in the stools in some cases of intestinal allergy

The release of histamine undoubtedly can be accomplished by other mechanisms than allergy (cold trauma burns and possibly psychogenic factors) and it is possible that some so called allergic manifestations may be produced without allergy Furthermore the allergic reaction produces effects in addition to histamine liberation

RATIONALE OF TREATMENT

The rationale on which various types of therapy are based should be understood

normal intelligence makes the approach difficult if not impossible

Purpose of Psychotherapy

Psychotherapy is an effort to understand the personality structure of patients, the mental mechanisms which are at work, and the specific relationships of psychologic situations in the precipitation of the illness This knowledge is utilized to promote the patient s emotional development so that no longer does he have to find the answer to his problems through illness Thus, instead of treating symptoms we try to improve the patient s emotional adjustment in order that his symptoms will no longer be necessary to him What the physician nurse, and social worker may mean to the patient in terms of emotional significance is an integral part of this procedure

Reassurance

Reassurance in the majority of instances unless combined with an analysis of the illness from the standpoint of the behavior, gives only temporary help and, depending upon the degree of anxiety has to be constantly repeated like a dose of digitalis for a failing heart

DEEP PSYCHOTHERAPY

Real psychotherapy, which is the direc opposite of simple reassurance, tries t make the patient understand the meaning of his symptoms and the nature of his conflicts It is a re educational process and when properly carried out leads to sufficient emotional development so that the necessity for symptom formation is abolished It may be defined as a process which utilizes psychodynamic principles to bring about emotional growth thus permitting greater development of the individual s capacities and better social adjustment

The best example of psychotherapy is psychoanalysis, but for various reasons this method cannot be applied directly to the majority of patients Nevertheless psychoanalytic insight and guidance in management, combined with re education and reassurance prove adequate to handle the emotional factor in the majority of psychosomatic disturbances Between simple reassurance at one end of the scale and adequate psychoanalysis at the other, there are all degrees of psychotherapy which can be applied depending upon the degree of illness and the circumstances of the patient

or to provide diets relevant to each However the major principles will be presented with the suggestion that when specific details are required the reader should consult appropriate reference sources There is no particular difficulty (except lack of will power) in avoiding many foods, such as various fruits vegetables, nuts fish, meats and most cereal grains Since these foods rarely pose under other guises the consumer knows when he is being served them

On the other hand certain foods, such as egg wheat milk and condiments are such common ingredients of prepared foods that one is faced with a real problem when their avoidance becomes advisable In such instances specific and detailed diets must be furnished to the patient if such foods are to be eliminated

The strictness with which a particular food should be avoided depends on several factors In diagnostic procedures complete avoidance is desirable otherwise, a negative result may cause doubt The merest traces of certain foods may be responsible for clinical manifestations for example, nuts eggs, fish and cottonseed It is not an uncommon occurrence for allergic symptoms to be produced by the odors of frying egg or even the smell of raw fish However, in most instances of food allergy there is a reasonable degree of tolerance so that simple methods of avoidance without going to the extreme and difficult task of avoiding traces usually are sufficient for therapeutic procedures The history provided by the patient may give a clue as to the strictness required in the diet

The allergenic qualities of foods are modified to some extent by heat Thus in some instances the boiling of milk (in a double boiler) for a long time, the use of dry milk and the cooking of fruits or vegetables will modify the allergenic potentialities so that they may be tolerated Not all portions of foods are equally allergenic Some patients who are allergic to peaches for example, may be able to eat the latter if the skin is removed

In certain quarters there has evolved an overemphasis on various aspects of food allergy For example, the merest infinitesimal and theoretical trace of such a food in the finished product is regarded as a potent antigen According to this school corn is the most violent of all food allergens (contrary to many years of observation on the part of many allergists of large experience) Furthermore, according to this group such products of corn as corn syrup corn starch and even pure dextrose are responsible for many cases of allergy At this time there is not any satisfactory evidence to support these claims

Environmental Allergens

Allergenic substances in the home place of work, and the outdoors can frequently be eliminated. In the home this may mean getting rid of a cat or dog or it may mean leaving the riding habit in the basement or in the stables so as not to expose the allergic member of the family to his exciting factor In some instances of cow hair sensitivity it may be necessary to dispense with the felt carpet padding Hair setting fluid may have to be changed a pillow or mattress may have to be changed or covered plants may have to be removed and a change of cosmetics may have to be instituted Hypoallergenic cosmetics often provide a solution for those who are sensitive to some cosmetic ingredients A list of such cosmetics can be obtained from the Committee on Cosmetics of the American Medical Association

Occupational allergy not infrequently is so difficult to handle that a change of occupation may be indicated This may apply to bakers horse or other animal attendants gardeners and workers in some of the chemical industries such as penicillin manufacturing dyes and other chemicals

Treatment in allergy can vary because it may be directed toward any of several points in the chain of events producing symptoms

1 The antigen and reagin can be prevented from uniting by the production of an immunizing or blocking antibody which interposes between the antigen and the sensitizing antibody This is accomplished by desensitization (such as in pollen treatment) The failure of the antigen and reagin to unite will prevent the release of histamine

2 Increasing the tolerance to histamine has been attempted by injections of histamine or histamine azoprotein The evidence indicates that such tolerance is not achieved

3 Histamine presumably could be destroyed by the enzyme histaminase However, the amount of such histaminase and the duration of action required are feasible in vivo

4 Certain chemical substances (such benadryl," or 'pyribenzamine') can compete with histamine for the cell receptor

5 After the histamine has produced typical pharmacologic effects, certain drug can correct or improve these effects Thus vasoconstrictors (ephedrine, epinephrine) will help correct the vasodilatation and edema Bronchodilators (aminophylline, epinephrine, nitrites) will relax smooth muscle spasms Iodides will modify mucous gland dysfunction Sedatives will overcome excitation and apprehensiveness

Treatment in allergic manifestations is comprised generally of two phases treatment designed to relieve the patient of an individual allergic attack, and treatment which aims to improve the patient in general so that his state is less troublesome

General Treatment

THIS consists essentially of measures designed either to remove the causative allergen from the allergic patient or to attempt to increase his tolerance to it when avoidance is not practicable

AVOIDANCE OF ALLERGENS

Foods

Some physicians believe that there is no phenomenon such as food allergy Others see food allergy in every allergic manifestation Obviously both attitudes are incorrect In the present state of our knowledge concerning this subject a practical and commonsense point of view must be taken toward food allergy If positive skin reactions to food tests provide a diagnostic lead, special diet is prescribed If skin tests are negative the presence or absence of food allergy can be ascertained by prescribing simple restricted diets, which can be changed in a few days if advisable Such a diagnostic diet will vary depending on the particular allergic manifestation and factors elicited in the patient's history

In asthma for example, such a diagnostic diet will often be a wheat, egg, and milk free diet usually followed for ten days If satisfying results are not observed, the exact reverse of the preceding diet is tried. A diet composed solely of milk and milk products may yield a quick clue Because this chapter must conserve space for discussion of therapy, the reader is advised to refer to other sources for details of diagnostic diets

When a food allergy is diagnosed the practical problem of avoidance presents itself It will not be possible in one chapter to give details of avoidance of each food

breathing In such cases the air would either leak around the points of contact of the mask with the face or, failing to do so the mask would have to be removed In either event the purpose of filtration would be defeated The simplest masks are the most dependable and most practical There is not any advantage in special devices such as equipment with batteries

Nasal filters also have been used The author s experience indicates that many of these filters are equipped with filtering media having openings or pores several times the size of pollen Others have such a dense medium that only slight moisture from the nose is sufficient to make them completely nonpermeable to air It is our impression that when relief is obtained by these nasal gadgets it is not due to filtration but to the mechanical separation of the turbinate from the septum by the stretching force of the frame of the filter

Gloves When allergy is due to contact substances, such as plants, penicillin and streptomycin it may be necessary to instruct the sensitive person to use rubber gloves in the handling of such materials Gloves made of cellophane also have been used for this purpose Recently a skin dressing* has been prepared whose protective proper ties are based on depositing a molecular film of an inert substance, silicone

Climate and Resorts

The question of a change of climate because of an allergic state is one of the most frequent therapeutic procedures con templated by the patient and his physician It is also one of the most misconstrued fea tures concerning asthma and other allergy There are by far too many unnecessary migrations in which the victim either does not obtain relief or when the relief ob tained could have been secured at home with much less sacrifice In considering the necessity for, or the location of a climatic change, the rationale of the *principles of* benefit from climate and the individual patient s problem must be evaluated The following are several ways a change of climate may operate

1 **Environmental Change Unrelated to Climate** Many persons have needlessly left their homes for better ' climates tem porarily or permanently when the cause of their allergy could have been eliminated easily at home It is unnecessary to go to Arizona or California because a dog in the home, or a feather pillow or house dust, or an occupational exposure, or allergy to wheat is responsible for the asthma Proper diagnostic procedures and observations will avoid making such useless climatic maneu vers

2 **Absent or Diminished Air Borne Allergens** In many instances of seasonal asthma, hay fever, and other allergy it is possible to predict that a change to a specific locality will result in diminished exposure to such allergens As a corollary it may be as readily forecast that other con templated localities will not do any good and in some instances may aggravate the condition For example, a number of local ities are free or almost free from ragweed pollen Among these are the Portland (Oregon) area the Seattle area, Miami (Florida) Los Angeles, Glacier National Park, Estes Park, Yellowstone Park, Sun Valley (Idaho), and most areas outside the United States Not entirely free but gen erally satisfactory are such places as Isle Royale some areas in the White Moun tains, and much of the forested areas in the northernmost part of Minnesota and the Ontario area adjacent to it

Mold allergy in the United States occurs generally speaking in the ragweed belt. However, the association is not an absolute one There are a number of localities where the ragweed problem is negligible or absent and yet mold allergy exists although

* Manufactured by Abbott Laboratories North Chicago Illinois

Contact Barriers between Allergen and Patient

In some instances of respiratory allergy or contact dermatitis effective results may be possible by interposing a barrier between the allergen and the patient.

Dustproof Casings. A dustproof casing (a list of such casings can be obtained from the Council on Physical Medicine and Re-habilitation of the American Medical Asso-ation), usually made of rubberized aterial employed for the pillow contain feathers is as a rule the only procedure ded in an instance of allergy to feathers source of the allergen in house dust allergy is primarily the cotton linter which is commonly employed in the stuffing of mattresses and furniture Since the pa-tient's mattress constitutes a source of a considerable portion of the dust inhaled it is wise to have the mattress and box spring inclosed in such dust proof casings In some instances the patient may prefer to change to a pillow and mattress made of sponge rubber (latex) It is impractical to attempt to treat the furniture in like man-ner

If the dust allergy does not respond to these simple measures and the use of com-mon sense in avoiding dust, it is not prac-ticable to go to extremes of dust avoidance, such as the use of unupholstered furniture bare floors, and drapeless windows In such instances it is best to proceed with de-ensitization measures

Filters Home filters are used to cut own the amount of air borne particles hich originate primarily outdoors, par-ularly pollen and mold spores In the al arrangement the filtration system is ced in the air intake which serves the re home In the more commonly used me the filtering apparatus is connected a window in the patient's own room principal parts of such a mechanism filtering medium through which the sucked in by a fan with reverse blades

Some apparatus also provide cooling T efficiency of different makes of appara varies considerably, and it is important th the efficiency be ascertained from unbias sources before it is recommended to th patient (Information may be obtaine from the Council on Physical Medicin and Rehabilitation of the American Med ical Association)

With a special apparatus which makes use of the principle of attraction of air particles to plates which have a high electrostatic charge, as an addition to the filtration mechanism, even more effective air cleaning can be accomplished If the air pressure in the room is increased with the filter it is possible for the air currents to move chiefly outward from the room through the slight openings in the windows and door so that to a reasonable degree dusts from the remainder of the house can be excluded

Generally speaking, however, too much is expected from such filters For example in the case of pollen and molds most of the exposure occurs during the daylight hours Actually, the amount of such outdoor particles to which the patient is exposed during the night in his bedroom without a filter is about 5 to 20 per cent of the amount to which he could be exposed during the twenty four hour period under normal conditions One cannot expect too much benefit from a measure di-rected to only a fraction of the sufferer's allergenic load. If the patient is willing to live most of the time in the prepared room the results can, of course, be much better

Face Masks and Filters Face masks may be helpful in keeping out some of the air borne dust such as pollen, mold spores house dust, and occupational dusts The filtering medium must not be too permeable nor too dense If the filter material is too dense the negative pressure from inspiration may not be sufficient for proper

able) influence on the mental state Escaping a troubled domestic life, a difficult situation in one's work, or a social complex, may affect the patient sufficiently to cause improvement in his asthmatic state The rest and relaxation accompanying such a change may be responsible Usually these goals can be accomplished without sending the patient to distant places or to seek particular climates In some instances of this type, however the effect of a climatic change is in some unexplainable way beneficial in itself

6 Unexplained Benefit Although explanations are not available there are allergic persons not in the above categories *who benefit from a change of climate* One can only say that if a patient with asthma or rhinitis has exhausted the usual possibilities at hand at home and if the severity of the condition justifies it, a trial at climatic change is indicated But because *in such instances as in others*, such a change may be utterly fruitless it is important that a permanent move be not made until a testing residence in the territory considered has been tried first

DESENSITIZATION

Increasing the tolerance of the allergic person to a specific allergen constitutes desensitization The object of desensitization is to enable the patient to tolerate his expected exposure dose of the allergen Complete desensitization which would enable one to tolerate any amount of the allergen (for instance the inhalation of a handful *of pollen powder*) is not necessary nor is it likely to be achieved Indeed, in many instances it is difficult to obtain the degree of immunity required to afford protection against some clinical exposures

General Procedure The general scheme entails an exposure to small measured and relatively harmless amounts of the specific allergen at regular intervals increasing the amounts as tolerance increases

For inhalants the procedure is essentially as follows The initial dose is small (for example, 05 cc of 1 10 000 or 1 100 000 dilution in the case of pollen in the average patient) and is usually given subcutaneously In a few days another injection of an increased amount is given, usually about 25 to 50 per cent increase if the response from the preceding dose has been satisfactory, i e absence of any systemic symptoms (hay fever, urticaria, etc) and of excessive local swelling If there is negligible local response the increments can be greater If there is too much reaction the dose either is not increased or is decreased

The increments in volume are continued *until a dose of about* 1 cc. is reached *Then* a more concentrated solution is used, usually a concentration ten times greater than the preceding one Small volumes are again employed with the new solution and increments made as previously As the dose becomes larger the *percentage* of increment becomes smaller The maximum dose is one which has produced adequate results or for prophylactic or preseasonal treatment a dose which has been found to be satisfactory for the majority When maximal doses are reached the intervals are usually increased maintenance doses customarily being administered at intervals of two weeks or even longer

Who Should Be Desensitized? Desensitization is carried out primarily with agents that are inhaled Hypodermic desensitization against foods is not an accepted procedure In some instances of contact or bacterial allergy desensitization may *be em*ployed The majority of inhalants do not require desensitization because they can either be eliminated or reduced in the environment Desensitization to inhalants therefore is indicated only when the degree of necessary exposure is sufficient to *maintain annoying allergic* symptoms The antigens which are most applicable for de

usually not as intensively as in the ragweed belt Among such localities may be included the west coast, parts of Arizona, the southern part of Florida and, of course, many parts of the world outside the United States

Grass pollen cases also have difficulty in finding a locality suitable for them The general types of territories favorable to them are high altitudes arid climates, and semitropical or tropical areas

It is important to remember that although a climatic change may provide complete relief for the allergic person, residence in such a climate does not permanently rid him of his allergy Even after an absence of several years a return to his former home or neighborhood will usually produce a recurrence of symptoms

3 **Freedom from Undesirable Features Other than Allergens** A number of atmospheric conditions other than the presence of the specific allergen may affect a respiratory allergy The soot and coal gases of city smoke are common irritants Often the suburbanite leaving his home feeling well sniffles, coughs, and wheezes by the time he reaches the city This is an atmospheric condition but not climatic It is not necessary nor advisable for such a person to move far away In some localities the dry soil dust acts mechanically as an irritant in respiratory allergy One may for example actually witness the seeming paradox of an individual from the dust bowl of Kansas or the dry dusty rural territory of Arizona obtaining benefit to his asthma on moving to Chicago or Cleveland

Humidity is another important factor Many patients with asthma are affected adversely by increased humidity, and a dry climate may be beneficial Similarly, those whose condition is aggravated by low temperatures or marked changes in temperature may benefit in warmer climates Other atmospheric conditions, such as barometric pressure or ionization, may play a part.

However, while in some patients atmospheric conditions appear to be responsible for the allergic symptoms, the majority are unaffected by these factors if their allergy is determined and adjusted Hence, it is improper to exile such patients before a serious attempt has been made to approach the underlying allergy which probably is present

4 **Effects of Climate on Infectious Process** If the patient s asthma is due primarily to bronchitis it is possible that a more favorable climate will benefit him If he has an allergic asthma which has become complicated by bronchitis again he may be benefited When contemplating the advisability of a change one must weigh several factors, such as the benefit that can be obtained at home by allergic management and/or the treatment of the infectious process, and the severity of the bronchitis

Similar considerations hold true for the nasal allergy which has become complicated by sinus infection If the author s experience with patients with respiratory allergy who have been observed previously by general practitioners and pediatricians, reflects the prevailing attitude, it is quite obvious that a diagnosis of respiratory infection is too frequently made without sufficient supporting evidence The major criteria for the presence of such infection are a suggestive history (cough, fever, etc, antedating the asthma) the presence of muco purulent sputum (or nasal secretions) without eosinophiles, and the absence of positive findings from study directed towards obtaining information on allergy Mere failure to identify a specific allergy does not permit classification of such a patient as having an infectious process

5 **Psychosomatic Influence** A change of environment or change of climate may exert a favorable (or sometimes unfavor

Aug	2	Ragweed 1 33	41 cc	
	5	Ragweed 1 33	45 cc	
	9	Ragweed 1 33	50 cc	
	12	Ragweed 1 33	55 cc	
	16	Ragweed 1 33	60 cc	
	20	Ragweed 1 33	40 cc	(pollen in air slight symptoms dose reduced)
	27	Ragweed 1 33	30 cc	
Sept	3	Ragweed 1 33	30 cc	(some discomfort anti histaminic drug prescribed to be used as needed)
	9	Ragweed 1 33	30 cc	
	16	Ragweed 1 33	30 cc	
	23	Ragweed 1 33	30 cc	
Oct	7	Ragweed 1 33	30 cc	
	21	Ragweed 1 33	33 cc	(season over, Patient begun on perennial treatments)
Nov	4	Ragweed 1 33	36 cc	
	19	Ragweed 1 33	39 cc	
Dec	2	Ragweed 1 33	42 cc	
	16	Ragweed 1 33	45 cc	
	30	Ragweed 1 33	48 cc	
Jan	3	Ragweed 1 33	51 cc	
	27	Ragweed 1 33	55 cc	
Feb	10	Ragweed 1 33	60 cc	
	24	Ragweed 1 33	65 cc	

Constitutional Reactions Constitutional reactions may occur during desensitization and may vary from mild nasal congestion and hay fever, slight urticaria, itching or slight wheezing to more severe asthma, generalized urticaria, and even intestinal or uterine contractions or more severe reactions associated with signs of shock The anaphylactic type of reaction on rare occasions may terminate fatally

The severe reactions can usually be avoided and the mild reactions can be minimized by observing certain precautions Any systemic reaction is an expression of a titer of the antigen in the blood which the patient is unable to tolerate This may occur as a result of any of several reasons The dose administered may be too large in itself, the antigen may pass into a blood vessel and the titer greatly increased, or the tolerance of the individual may be diminished at the time of the injection

To minimize reactions a careful schedule of doses is important The initial doses should not be too large The subsequent dose should not be increased if the local swelling is larger than the size of a walnut. If the interval between treatments has been longer than two or three weeks the dose should not be increased and if much longer it should be diminished While rules can not be formulated, a lapse of a month would on the average justify 25 per cent reduction, two months, 75 per cent reduction, three months, 90 per cent, and four months, the beginning dose During the hay fever season the maximal doses should be reduced, in some instances two-thirds or one half, in others to much less Concentrated solutions preferably should not be given in small volumes (such as 0 05 or 0 1 cc) since small volumes are more rapidly absorbed

The most severe systemic reactions are apt to result from the accidental entrance of the antigen solution into a blood vessel The following precautions will minimize the possibility of such an accident After the needle is inserted subcutaneously the plunger is retracted, if blood is not withdrawn a small amount of the liquid (0 01-0 02 cc) is injected and the plunger again retracted The small amount of liquid will insure the patency of the needle in case the latter has become obstructed after inserting it into the tissues If blood is not withdrawn on the second attempt, the solution is slowly injected In most instances and particularly for those whose experience has not been extensive, it is wise for the patient to remain for a few minutes under observation For patients who have a tendency to repeated reactions, a dose of an anti

sensitization purposes are pollen, molds and house dust In a few special instances desensitization is advisable to horse dander, cow dander, dog dander and other animal danders which may constitute occupational problems Other occupational dusts may at times require desensitization

Dosage Schedule A dosage schedule can never be a fixed one The dosages, minimal, maximal and the rate of increase will depend on a number of variables such s the nature of the allergen the method f its preparation the degree of sensitivity the particular person and the facility of protective response the degree of nat l exposure to the allergen the absence presence of exposure at the time of treat nt and the period available prior to osure

Potent allergens such as horse dander should ordinarily be used initially in dilu tions of 1 100 000 or 1 1 000 000 Purified house dust extract is usually employed in 1 100 000 dilution as the initial concentra tion while the dust extract made by the average office or commercial laboratory would possess potency of about 1 100 (in terms of the original crude dust) For pollen allergy the average person can be gin with a concentration of 1 10 000 Many however require a 1 100 000 dilution and occasionally a 1 1 000 000 is necessary Irre spective of the initial dose tolerated the grade of the curve of increment of dosage will vary because of the marked differences in capability of developing tolerance In Chicago one requires greater protection and a higher dose) against ragweed and mold than one would require in Boston hereas in Des Moines Iowa one would quire greater protection than in Chicago arger doses are tolerated prior to the ason or prior to exposure

Table 25 shows the usual beginning d maximal doses of several antigens as ployed in patients in the Chicago area

TABLE 25 ANTIGEN DOSES CHICAGO ARE

	Beginning dose	*Maximal do*
Ragweed	05 cc of 1 10 000 (5 pollen units or 2 5 protein nitrogen units)	5 cc of 1 (15 000 pol units or 75 protein nitrog units)
Molds	05 cc of 1 10 000	6 cc of 1 50
House dust	05 cc. of 1 100 000	5 cc of 1 1000

To visualize a treatment schedule in operation a typical program is presented below for an average ragweed case The schedule is an actual record of a patient s treatment

April 5	Ragweed 1 10 000	05 cc	
8	Ragweed 1 10 000	10 cc	
12	Ragweed 1 10 000	15 cc	
15	Ragweed 1 10 000	25 cc.	
19	Ragweed 1 10,000	35 cc.	
23	Ragweed 1 10 000	50 cc	
26	Ragweed 1 10 000	70 cc	(considerable local reac tion)
29	Ragweed 1 10 000	70 cc	
May 4	Ragweed 1 10 000	1 0 cc	
7	Ragweed 1 1 000	15 cc	
10	Ragweed 1 1 000	25 cc	
13	Ragweed 1 1 000	35 cc	
17	Ragweed 1 1,000	50 cc	
20	Ragweed 1 1 000	70 cc	
24	Ragweed 1 1 000	1 0 cc	
28	Ragweed 1 100	15 cc	
June 4	Ragweed 1 100	20 cc	
7	Ragweed 1 100	25 cc	
8	Ragweed 1 100	30 cc	(considerable local reac- tion)
11	Ragweed 1 100	30 cc	
15	Ragweed 1 100	35 cc	
18	Ragweed 1 100	40 cc	
21	Ragweed 1 100	50 cc	
25	Ragweed 1 100	60 cc	
28	Ragweed 1 100	70 cc	(considerable local reac tion)
July 6	Ragweed 1 100	70 cc	(considerable local reac- tion)
9	Ragweed 1 100	70 cc	
13	Ragweed 1 100	75 cc.	
16	Ragweed 1 100	80 cc	
20	Ragweed 1 100	85 cc	
23	Ragweed 1 100	95 cc	
26	Ragweed 1 33	35 cc	
30	Ragweed 1 33	38 cc.	

hydrochloride solution These topical applications may be used in the form of nose drops or spray, or inhaler

Vasoconstricting drops should be employed with caution, particularly when they are used repeatedly and over a protracted period as there is a tendency for increased compensatory congestion and swelling every time the constricting effect of the drug wears off This results in further use of the drug and a continued repetition of the process Finally the patient is using the vasoconstricting drops at frequent intervals simply because of the post congestive effect of its vasoconstrictor action, the original cause of the nasal congestion having disappeared weeks, months, or even years before This effect is more apt to occur following use of the more potent vasoconstrictors such as privine and "neo-synephrin' If such a situation is reached or suspected the patient should discontinue immediately all vasoconstricting nose drops He may require sedatives at night

In the daytime and at bedtime antihistaminic medication orally may be helpful Histaclopane orally has been helpful in resistant cases In some instances the additional effect of a spray of 'pyribenzamine 0 5–2 per cent administered with a nebulizer (e g, DeVilbiss No 40) with a nasal attachment may give added relief

Usually after two or three days of such management definite improvement in the nasal condition results The topical application of pyribenzamine either in the form of the spray (2 per cent) or in the form of nose drops (0 5 per cent) preferably the former may be a useful symptomatic remedy in itself for the relief of hay fever and nonseasonal allergic rhinitis The fine spray is not irritating to the majority of patients and since it does not have any direct constricting effect it can be used at frequent intervals

For itching and burning of the eyes a wash or drops of boric acid solution may be sufficient Cold compresses are also helpful For more intense congestion and itching a drop of 1 10 000 or 1 5000 solution of epinephrine is indicated The following eye drops will often give pleasant relief

	Gm or cc
'Holocaine' hydrochloride	0 1
Epinephrine 1 1000	3 0
Isotonic sodium chloride solution to make	15 0

Vasoconstrictors by Mouth

Ephedrine hydrochloride or sulfate in 25 mg doses often helps the nasal symptoms If the natural ephedrine is not well tolerated the synthetic racemic ephedrine (racephedrine) may be used If the latter is objectionable, 'propadrine hydrochloride 25–50 mg, may be substituted Histaclopane is useful particularly if nasal stuffiness is a prominent symptom

Antihistaminic Drugs

Within the last few years a number of compounds have been synthesized to compete with the histamine which is liberated in the allergic reaction and which presumably is responsible for most of the changes resulting in some allergic manifestations These drugs as a class are useful in nasal allergy They are most helpful in the relief of sneezing and nasal itching, but also are helpful in reducing the coryza and are of aid in controlling the nasal edema The acute symptoms of allergic rhinitis respond better than the chronic cases with persistent intumescence of the turbinates The effect of a single dose of most of the drugs persists for three or four hours In many instances where the mild symptoms are relieved the severe symptoms may be unaffected Thus the results are influenced by the severity of the nasal symptoms the stage of the hay fever season (it is more difficult to obtain relief during the postseasonal congestive stage), the severity of the season

histaminic drug one hour prior to the injection may diminish the tendency In some instances it is advisable to add 0 2 cc of 1 1000 epinephrine solution to the treatment dose Current research may make it possible to further minimize reaction by modification of antigens to slow their absorption or to make them less reactive

Mild reactions will usually occur fifteen minutes to several hours after the injection They usually do not require medication and will disappear in a few hours If the symptoms are disturbing a dose of ephed ine or an antihistaminic drug will usually e sufficient to obtain relief If more severe eactions occur an injection of epineph ne may be required If very severe or if reaction occurs immediately after the in tion epinephrine 0 5 cc of 1 1000 should immediately administered in the oppo site arm and a tourniquet applied to the arm which had received the antigen If re lief does not occur in five minutes the epinephrine injection should be repeated If these measures do not suffice aminophyl line intravenously should be administered and oxygen inhalation may be advisable if asphyxia is pronounced For treatment of shock symptoms caffeine sodium ben zoate intramuscularly is indicated

Results of Desensitization The ma ity of patients achieve reasonable tolera by desensitization sufficient to protect th under conditions occurring most of t time in their environment After son period of treatment, say one to sever years some lasting tolerance may resul the duration of which may be a few month to a few years Some patients apparently acquire permanent protection Newer methods may shorten the procedure of desensitization and produce even more last ing results

In some instances of food allergy at tempts at desensitization may be justified This may be advisable for such foods as egg wheat or milk The procedure con sists of taking small doses of the food by mouth one or two times daily For example in the case of wheat one might start with a puffed wheat grain which is increased by one or two each time until a teaspoonful dose is reached Then the increments may be in fractions of a teaspoonful and later in tablespoonful amounts Still later seg ments of toast measured in square inches may be used until a dose of a slice of bread is reached To arrive at the usual portion of such a food may require two to four months

Symptomatic and Special Treatment

IAY FEVER AND PERENNIAL LLERGIC RHINITIS

In the vast majority of instances of sea nal hay fever one can demonstrate a ecific etiologic factor In the perennial iety of vasomotor rhinitis an allergic ology often cannot be determined ertheless the symptomatic treatment is ntially identical for both types of aller manifestations

Topical Applications

Many varieties of vasoconstricting drugs exist Among the best known at the time this chapter is written are the following, in the approximate order of increasing in tensity of action paredrine hydrobromide solution 'propadrine hydrochloride solution benzedrex (amphetamine) in haler ephedrine hydrochloride solution neo-synephrin' solution and "privine

(Burroughs Welcome) 50 mg Effective slightly sedative

Other compounds on the market include

Tagathen (Lederle) 50 mg Effective moderately sedative

Histadyl (Methapyrilene — Eli Lilly and Co) 50–100 mg Effective, moderately sedative

Thephorin (Hoffman LaRoche) 25–50 mg Effective, stimulating

Phenergan (Wyeth) 12 5–25 mg Highly effective but very highly sedative

Chlor trimeton (Schering) 4 mg Effective moderately sedative 'Thenfadil (Winthrop-Stearns)

Although the antihistaminic drugs vary in their index of potency and sedation a patient may deviate from the usual in his response to a particular drug Thus one drug which produces better results in one person may cause different effects in another

Unless removal to an effective resort is practicable the majority of hay fever patients should have desensitization treatment The antihistaminic drugs may be of great aid, but seldom are they sufficient in themselves A sufferer who has achieved reasonable tolerance to pollen by desensitization may still require the use of a dose of an antihistamine now and then as an adjunct In such cases however, the drug is more effective than without desensitization In other words desensitization plus an antihistamine when needed gives the most effective results

Specific Treatment

Since the principles of desensitization in general already have been discussed we will only emphasize briefly the points pertaining to hay fever

Pollens to Be Selected One should not treat for skin reactions The choice of pollen to be used in treatment depends on the following criteria all of which must be met before it is selected

(1) Pollination time must agree with the season of the patient s symptoms A midwestern hay fever sufferer having symptoms from the middle of August to the end of September should not have grass pollen added to his treatment

(2) The type of plant must be indigenous to the locality, for example Johnson grass pollen should not be administered to a midwestern patient because this particular grass is a southern variety and the patient is hundreds of miles away from such pollen

(3) The pollen must be wind borne There is not any necessity for treating with aster or goldenrod pollen and other insect borne pollen

(4) Plants must be present in abundance or sufficient pollen should be demonstrated in the air A few stray plants of hemp or several birch trees in Chicago for example do not create a hay fever problem

(5) The patient should exhibit a positive skin test or other evidence of sensitivity to the pollen in question

Potency and Reliability of Pollen Extracts For the vast majority who will procure their extracts from pharmaceutical houses one can only caution that a well known reliable house be selected If one has the facilities and ability to prepare his own pollen extracts, standard texts will guide him The extracts should be refrigerated most of the time The more dilute extracts lose potency more frequently than the concentrated

Schemes of Treatment *Preseasonal* treatment is perhaps most common Usually the treatment is begun twelve to sixteen weeks prior to the season If begun earlier or later the schedule is modified The patient customarily appears for injections twice weekly The initial and maximal doses have been discussed previously in this chapter As soon as there is more than a stray pollen in the air the dose is reduced by one third or one half in most instances The dose is given weekly to be discon

the type of hay fever (ragweed is more difficult to control than grass), and the locale of the patient (ragweed cases for example, are easier to relieve in Boston or New York than in Indianapolis)

Most of these drugs are usually prescribed in 50 mg doses as needed In many cases of nasal allergy only a morning or bedtime dose is required When the symptoms are more or less continuous about four daily loses may be advisable The dose should e regulated according to the severity of ie symptoms the more severe symptoms quiring larger amounts of the drug Chil en and infants will require smaller doses hough they often tolerate antihistaminic igs better than the adults For young ldren syrups or elixirs are commonly ployed In most instances these drugs are tolerated better after meals

Limitation of the Antihistamines. Because of promotional publicity and uncritical reports concerning these drugs, certain vital features of their action have frequently been overlooked The limitations of these compounds are real (1) They do not affect all varieties of allergic manifestations (2) they do not help all phases of a single allergy (for example the asthma associated with hay fever is influenced little) (3) they do not eliminate a single symptom completely in most instances Since the principle of the mechanism of action of the antihistaminic drug is production of a balance between itself and histamine on the cell a large part of the latter will always remain active unless it were possible to employ extremely large loses which cannot be done with presently vailable drugs (4) no doubt there are fects of the allergic reaction other than stamine action and the antihistaminic ugs cannot be expected to correct these ects (5) there is evidence that some de e of tolerance occurs after frequent use hese drugs (6) the drugs are limited in r use because of undesirable side-effects

the most common of which is seda which may at times be intense Dizzi is another common complaint Lassitu inability to concentrate and poor coordi tion are not infrequent effects Gastro testinal symptoms are rather common th include loss of appetite gastric discomfor nausea abdominal pain and diarrhea Ur comfortable dryness of the nose, mouth and throat may occur Headache is seen on occasion In some patients excitatory effects are noted and insomnia, nervousness and palpitation may result More serious reactions have been mentioned from time to time but visceral damage from these drugs is extremely rare

At the time of this writing the following antihistaminic drugs have been accepted by the Council of Pharmacy and Chemistry of the American Medical Association Their average doses and chief characteristics are noted

Diphenhydramine (benadryl —Parke, Davis) hydrochloride 50 mg Effective, but has high sedative tendency

Tripelennamine (pyribenzamine — Ciba) hydrochloride 50 mg Highly effective moderately sedative

Methapyrilene (thenylene — Abbott) hydrochloride 50–100 mg Effective moderately sedative

Metaphenilene (diatrine —Warner) hydrochloride 25–50 mg Moderately effective moderately sedative

Thonzylamine (Neohetramine — Nepera) hydrochloride 50–100 mg Moderately effective slightly sedative

Prophenpyridamine (trimeton —Sch ing) no salt 25–50 mg Effective, moderat sedative

Pyrilamine (neo antergan — Merc maleate 25–50 mg Effective, moderate sedative and often gastrointestinal irritan

Doxylamine (decapryn —Merrell) suc cinate 12 5–25 mg Highly effective bu very highly sedative

Antistine (Ciba) 100 mg Moderately effective, slightly sedative

Di Paralene (Abbott) and ·Perazil

The use of these drugs will be described more fully in the section dealing with the treatment of asthma

ASTHMA

As has been mentioned earlier, bronchial obstruction in a particular stage of an asthma attack is due to any or all of the *mechanical changes of bronchospasm, mu*cosal edema and plugging with tenacious mucus The effectiveness of a particular symptomatic remedy depends on the predominating mechanism of obstruction at the moment

For therapy and prognosis it may become important to identify the etiologic classification of the asthma concerned At least three types of asthma are recognized (1) the allergic type, (2) the bacterial type, and (3) the cardiac type

The bacterial type is generally separated from the extrinsic allergic type by a history of onset in middle or past middle age, a history of bronchitic cough preceding asthma by weeks, months, or even years the general absence of other atopic manifestations in the patient or in the family, the mucopurulent sputum with absence of eosinophiles, the absence of positive skin tests, and in *questionable instances*, by the therapeutic response to antibiotics

Cardiac asthma is caused primarily by hypertensive heart disease, coronary sclerosis or thrombosis, and syphilitic aortitis with involvement of the coronary ostia In favor of a diagnosis of cardiac asthma are the following factors History of onset of *asthma past middle life*, duration of asthma less than two years, absence of rhinitis or other forms of atopy or positive skin tests, presence of any of the *aforementioned car*diac disease and evidence of decompensation It is less difficult to rule out cardiac asthma than *to diagnose it It is obvious* that the mere association of the cardiac disease with asthma in the same individual does not prove that the one depends on the other *It is necessary to prove* decompensation before a diagnosis of cardiac asthma can be entertained seriously One procedure is to do circulation time tests *

The symptomatic treatment of noncardiac asthma is different for the patient with mild asthma than for the one with a severe and acute attack

Treatment of Mild Asthma

The remedies for the mild or ambulatory case are usually those which the physician can prescribe for self medication by the patient

Ephedrine Ephedrine hydrochloride or sulfate is one of the most common and most effective remedies The average dose is 25 mg orally and is usually combined with a small dose of *sedative*, such as phenobarbital, 'seconal," 'amytal, or nembutal" The barbiturate of choice depends *in part on experience* with the particular patient, with respect to the action of the ephedrine and barbiturates, and in part on *whether the sedation should* stress intensity of action, prolongation, or rapidity of onset Natural ephedrine may cause palpitation, insomnia, nervousness or difficulty in urination In such instances racephedrine *may be tolerated* better If the latter also is not well tolerated 'propadrine' hydrochloride, in doses of 25–50 mg may be substituted *The latter drug however*, is not as reliable in its therapeutic action

Xanthines Aminophylline or other xanthines by mouth has little effect but combined with ephedrine or racephedrine *it may synergistically* aid the latter Such well known combinations are 'tedral' rac ephedrine, and ephedrine with 'glucophylline ' *Aminophylline* rectally, in the form of suppositories or by rectal instillation of the solution, in doses of 0 5 gm is also a *useful home remedy for the production of* moderate bronchodilatation It is most effective when given prior to the acute attack

* See Chapter 48

TABLE 26 RAGWEED POLLEN STANDARDS

Dilution: Amount (cc)	Dilution: Strength	Pollen units	Total nitrogen (Fractions of mg per cc)		Protein nitrogen units
0.10	1:100 000	1	0.0001	0.13	0
0.05	1:10 000	5	.001	.065	2
0.10	1:10,000	10	.001	.13	5
0.50	1:10 000	50	.001	.65	25
1.0	1:10,000	100	.01	1.3	50
0.2	1:1,000	200	.01	2.6	100
0.5	1:1,000	500	.01	6.5	250
1.0	1:1,000	1,000	.1	13	500
0.2	1:100	2,000	.1	26	1,000
0.5	1:100	5 000	.1	65	2 500
1.0	1:100	10,000	.4	33	5 000
0.2	1:33	6,000	.4	2	3 000
0.5	1:33	15 000	.4	5	7 500
1.0	1:33	30,000	.4	10	15 000

...ed when the season is near its end The ...ment is then resumed the following year

Perennial treatment in most instances requires continuation with maximal or submaximal doses after the end of the season Although the schemes vary, one found satisfactory is as follows The submaximal dose is given every two weeks, and is increased gradually until the onset of the next season At the time the latter is reached the dose achieved is usually higher than in the preceding season

Coseasonal treatment consists of giving injections only during the season usually small but gradually increasing doses being used and given every day or two

The *coseasonal treatment* cannot be expected to be effective in most instances except in the low pollen areas or in seasons of protracted pollination For ragweed hay fever in the midwest for example, it is not a scheme of choice Of course if the patient presents himself without previous treatment coseasonal treatment is worth trying

The relative merits of the *preseasonal* and *perennial methods* are as follows The preseasonal is psychologically more acceptable because there is a long period of rest The perennial method gives greater flexibility for those who travel or who find frequent visits a burden This method generally produces a greater degree of protection, although one encounters persons in whom the reverse is true

Pollen Standards Three standards for measuring dosages are in use the weight volume or dilution method, the total nitrogen unit, and the protein nitrogen unit The author and a large percentage of allergists are of the opinion that the weight volume or dilution method is the simplest and as scientific as the others since there is not complete evidence confining the antigen to any particular fraction There is not an absolute conversion factor from one standard to another—it differs materially in species of pollen and in various batches of the same species However in an average ragweed extract the following are the approximate equivalents 10 pollen units = 5 protein nitrogen units = 13 total nitrogen units Table 26 may be used as a measure for comparison of ragweed extracts

ACTH and Cortisone *Corticotropin (ACTH) or cortisone* may be useful in severe hay fever whose season is comparatively short These hormones are not as effective in hay fever as they are in asthma, and are seldom indicated in the former

be repeated Patients who have had many injections of epinephrine previously, or in whom unusually severe attacks occur, may require as much as 1 cc Large doses, however, may cause severe reactions, such as palpitation, nervousness, and persistent headache

Epinephrine in oil has been employed extensively to obtain a prolongation of its action Pharmacologic and clinical experience indicates that the absorbability of epinephrine in such form is unpredictable In many patients it may be absorbed too slowly to produce relief, while in others the entire amount (2 mg to 1 cc ampoule) may be absorbed almost immediately, resulting in pronounced undesirable reactions If one desires to use epinephrine in oil he should precede it with an effective dose of the aqueous solution and then administer only about 0 5 mg (0 25 cc) of the oil preparation Epinephrine should either not be used or used with great caution if absolutely necessary in the presence of coronary sclerosis or occlusion and other serious cardiac diseases marked hypertension and hyperthyroidism and in persons who have been shown by experience to respond unfavorably to sympathomimetic drugs

Aminophylline Aminophylline intravenously is administered if the patient does not respond well to epinephrine if he requires too many doses of the latter or if he has a disease that precludes the use of epinephrine The dose is 0 25 Gm In some instances this dose may be doubled The intravenous injections may be given two or three times daily Aminophylline has also been used intramuscularly but its use in this manner may produce considerable irritation and inflammation of the local tissues

Sedation When the asthma has been prolonged and the patient is fatigued or apprehensive or has been overstimulated by the sympathomimetic drugs and aminophylline sedation becomes important Barbiturates are most frequently useful If barbiturates do not produce the desired effect, chloral hydrate may be tried. Morphine and other opiates should be used rarely if at all, in asthma In addition to causing addiction they may cause suppression of the evacuation of bronchial secretions which would aggravate the asthmatic state and which might result in disastrous effects

Demerol, while not as objectionable as morphine, also may inhibit removal of sputum It, too, is not devoid of the danger of addiction

Oxygen In the usual asthma attack anoxemia is not a problem and oxygen administration is not helpful If the patient shows evidence of cyanosis or other signs of anoxemia, oxygen is, of course indicated. A mixture of 20 per cent oxygen and 80 per cent helium is preferred to undiluted oxygen Because of its conservation of respiratory effort it may be helpful even in persistent asthma without anoxemia In some instances it may be administered periodically, for example, one hour in each five or six hours

Ether. If the status asthmaticus persists in spite of the above measures the rectal administration of ether is advisable From 90 cc to 100 cc of ether is mixed with warmed olive or corn oil and the mixture is slowly instilled rectally with a small rubber catheter This usually permits the patient to sleep An additional dose of 30-45 cc of ether may be administered every three or four hours if the patient is awake and the asthma is not relieved Such sedation may be continued for twenty four hours During the period the asthmatic attack may cease If not it is at least likely that at the end of that period the patient will become responsive again to the usual remedies such as epinephrine and aminophylline

General Management During the treatment of a patient with a prolonged bout of asthma attention is directed too often entirely to the drugs and insufficient

for example, on retiring and prior to arising. Inhalation of aminophylline and theophylline aerosols and inhalation of theophylline dust also may relieve the attack.

If the asthmatic symptoms and the cough are persistent, *iodides* are usually helpful. Potassium iodide is prescribed in doses of 0.65 gm. three or four times daily after meals and at bedtime. The iodides will produce a freely flowing liquid expectoration. Apomorphine may help the expectorant action. The following combination has been used with good effect in several thousand cases:

	Gm or cc
Apomorphine hydrochloride	0.13
Potassium iodide	20.0
Syrup of cherry (N.F.) to make	120.0

Iodides are not tolerated well by some patients because of tendency for the development of acneiform eruptions or because of swelling of salivary glands.

Epinephrine. Inhalations of nebulized epinephrine 1:100 have a rapid effect in relieving moderate symptoms of asthma. An all-glass or plastic nebulizer (for example, DeVilbiss No. 40) is satisfactory and should be used. Usually one or two squeezes of the bulb is sufficient. This type of epinephrine medication has an advantage over the hypodermic route because few systemic symptoms (tachycardia, nervousness or insomnia) occur and the patient can treat his asthma early without waiting for the physician's visit. However, epinephrine inhalation is not as effective as the hypodermic injection in severe attacks.

Isopropylarterenol ("isuprel," "norisodrine") has been used as an inhalant with good results. A solution varying in strength from 1:200 up to 1:100 nebulized by the same type of nebulizer, gives results similar to those obtained with epinephrine. Usually larger quantities have to be employed. This drug is also available in the form of a diluted powder to be inhaled by means of a special device. This form of the drug is more effective in some instances. The advantages of this drug over epinephrine are that the former does not have a pressor action, is not a vasoconstrictor (shrinking or drying of throat and nose is absent), and in equal doses is less toxic than epinephrine. However, isopropylarterenol, like epinephrine is a powerful cardiac excitant. Excessive use of the drug by inhalation may produce sufficient absorption to result in uncomfortable and even dangerous cardiac overactivity. Sublingually or by injection this drug is too toxic and insufficiently effective in its bronchodilating action.

Asthma powders or cigarettes are useful home remedies. They generally contain stramonium leaves and nitrates, which when burned produce a smoke that has a bronchodilator effect. Their frequent use may, however, produce bronchial irritation.

The antihistaminic drugs have little effect on the acute asthma if they are used without other medication. If employed in association with ephedrine or epinephrine they may have some additive action. The spasmodic preasthmatic cough is, however, frequently amenable to antihistamine therapy. Aerosols of 2 per cent "pyribenzamine," or any other nonirritating antihistamine, relieve the cough even more frequently than the oral method, while some patients with asthma also are benefited by such medication.

Treatment of Severe Asthma Attack

If an acute attack of severe asthma does not respond to the medication previously outlined, other forms of treatment are indicated.

Epinephrine. Epinephrine hypodermically is the first choice in such treatment. The dose is usually 0.25 cc. administered intramuscularly or subcutaneously. If the attack is not relieved in five or ten minutes another injection of the same size should

picture further we have noted that in a particular person ACTH may be more effective at one time, while cortisone is more effective at another Where minimal maintenance doses (25–75 mg daily) are effective, it has been possible to administer the cortisone for months or even for a couple of years without ill effect

Nonspecific and Special Measures In this category one may include approaches which are not specifically immunologic or directed to the symptomatic relief of the attack Virtually hundreds of such procedures have been recommended or tried In this presentation we shall confine ourselves to those which are either most useful or most commonly advocated

Stock respiratory vaccines may be helpful when bacteria appear to be responsible for the asthma Treatment should be begun with small doses and increased carefully *Fever therapy* with physical apparatus typhoid injections or with piromen may produce a temporary remission but such treatment is not without hazard *Roentgen ray therapy* has helped in some instances *Penicillin inhalations* and *sulfonamides* have been effective in the acute stages of infectious asthma *Bronchoscopic aspiration* may at times be helpful in relieving a prolonged asthmatic state, although it is rarely indicated

Psychotherapy may constitute an important item of management in some patients It is necessary to avoid the prevailing tendency of ascribing everything which is strange difficult or undiagnosable to psychic origin The observant practitioner will usually recognize patients whose psychic problems play a part The greatest difficulty in handling these situations is the carrying out to completion of the therapeutic proposals Frustrations family difficulties and economic and occupational maladjustments often are insoluble

Tonsillectomy and other nose and throat surgery are not helpful usually in the treatment of asthma This is true also for appendectomies cholecystectomies or hysterectomies However, the absorption of traumatized tissues or the anesthetic may produce a temporary nonspecific relief of the asthma Surgery of infected sinuses may help to clear up an infectious asthma. In desperate situations various types of surgical procedures on the autonomic nervous system have been tried

Among other suggested remedies which have been found useless are potassium salts calcium salts, vitamins and most endocrine products In some instances postural drainage and breathing exercises may be useful.

URTICARIA, ANGIONEUROTIC EDEMA, AND SERUM SICKNESS

Urticaria and angioneurotic edema are essentially similar in etiology and pathology The angioneurotic edema lesions are deeper and may involve joints mucous membranes and viscera The urticarial lesions involve the upper skin layers and nerve endings and are characterized by itching An allergic factor can be identified in a fair percentage of these urticarial dermatoses Drugs such as aspirin phenacetin phenolphthalein and sulfonamides are among the most common causes Foods are specific allergens in a number of instances Among the most important foods are peaches strawberries fish nuts shellfish tomato and pork Abnormal response to *heat or cold may produce* these lesions Chronic foci of infection may account for some, and psychogenic factors for others *Unfortunately, however* there is not at present an identifiable cause for a large percentage The serum sickness occurring several days after *administration* of serum and the reactions following the use of sulfonamides or penicillin have many features in common with the *other urticarial* dermatoses and their treatment will be considered together

consideration is given to the general care of the sick individual Not infrequently the asthmatic patient is overtreated with drugs It may even be necessary because of the effects of the drugs to reduce drug therapy to an absolute minimum Rest and mental relaxation alone may be important factors in alleviating apprehension and tension This can be provided in a number of ways, for example music, reading companionship, and avoidance of disturbing visitors Convincing assurance from the physician and friends also are important items Administration of liquids frequently requires ttention since there is a tendency for the tient to limit fluid intake It may be ad able to give dextrose intravenously Feed may be an important problem, and liq foods high in carbohydrate content frequently administered sometimes are advisable In winter the addition of moisture to the room air may materially benefit the patient and shorten his attack.

ACTH and Cortisone Corticotropin (ACTH) and cortisone are effective remedies in the treatment of the acute severe status asthmaticus These hormones are to be used only when the usual remedies fail and when the condition appears to be alarming Since the effects of these agents are usually temporary they are not generally indicated in the chronic stage of the disease At any rate ACTH and cortisone should not be employed as a first line of attack in the treatment of asthma prior to the use of simpler remedies such as ephedrine epinephrine iodides and aminophylline and prior to any serious attempt to discover and correct the allergic cause the use of these agents may be contraindi ted in cardiac disease hypertension acne abetes psychoses and a number of other nditions During therapy the patient uld be limited in his sodium intake and assium salts may have to be adminis d in some instances If the use of these s is prolonged the patient should be observed particularly for possible e crinal changes

One of the hazards of ACTH and c tisone therapy is that the patient may more prone to sepsis because these h mones diminish localized inflammato phenomena which ordinarily would lim the spread of infection Another hazard i the diminution of signs of infection suc as pain and fever The presence of leukocytes during ACTH and cortisone therapy deprives the physician of a valuable diagnostic sign in the case of intercurrent infection It should also be added that acute allergic reactions to ACTH have been observed

The average initial dosage schedule of ACTH is 20 mg every six hours If improvement does not follow in twenty four hours the dose may be increased to 30–40 mg or even more When the effect has become almost maximal, which is usually in two or three days the dose may be gradually tapered, at first in amount and later in the intervals between doses Such a course of therapy usually lasts five to nine days In the event that it is desired to keep the patient on a maintenance dose for a more extended period the doses are reduced much more gradually, changes being made perhaps every three or four days. A slowly absorbing ACTH preparation may make it possible to administer the twenty four-hour dose in one or two injections

The principles involved in cortisone therapy are about the same as in the case of ACTH The initial daily dose is as a rule 0 2–0 3 Gm divided into two intramuscular injections or into four oral doses Tapering of doses is even more important with cortisone since sudden withdrawal may produce severe asthma and other symptoms due in part to lack of pituitary stimulation of cortical secretion In most instances we have found ACTH more effective than cortisone in asthma although in some patients the reverse is the rule To complicate the

since acute flaring of the eczema may follow an overdose of the antigen If the allergy is due to important foods an attempt to increase tolerance by oral desensitization is worthwhile In the presence of moderate food allergy avoidance of the causative food for a few months may be sufficient to permit increase of tolerance

Treatment

Topical therapy in general, including treatment with roentgen rays will be left to the chapter dealing with skin diseases (Chapter 38) However, it may be well to emphasize that in my experience topical applications of the antihistaminic drugs *have been additionally* helpful in the last few years While many drugs can be used, some are definitely more irritating than others On acutely inflamed skins and in some other situations practically any antihistamine locally may be irritating In addition to chemical irritation not infrequently an allergic contact dermatitis may result We have had the best experience with 'pyribenzamine' cream (water soluble) and ointment In most instances the water soluble cream is preferable and is customarily applied in 2 per cent concentration as often as desired provided the total dose of the drug does not exceed sytemic tolerance In most instances the itching is relieved, scratching minimized and the skin becomes less inflamed

Oral use of antihistaminic drugs often is helpful Usually the bedtime dose is the most important and in many instances this single dose is sufficient

CONTACT DERMATITIS

The identification and removal of the *responsible allergen is the most important* therapeutic step in this disease When the cause is of plant origin and the source is unavoidable such as in pollen dermatitis or plant dermatitis in gardeners hypodermic desensitization with allergenic extracts may be *helpful The antihistaminic drugs* orally and topically may give symptomatic relief

Treatment

Removal of an allergic cause is one of the first objectives Suspected drugs and suspected foods should be eliminated In persistent instances dietary restrictions should be instituted A milk diet for a few days may be the simplest approach to determine food allergy Other etiologic factors should be considered and adjusted

Antihistamines The most effective symptomatic therapy is the use of antihistaminic drugs The dose of the drug required is usually proportionate to the severity of the manifestations For example, some severe cases of angioneurotic edema which were not responsive to the antihistaminic drugs in the usual doses of 50 mg responded to doses of 150 mg It may be necessary to try several antihistamines in rapid succession before the most effective for the particular person is found

Other Drugs Ephedrine or epinephrine may be of use particularly for the acute symptoms When angioneurotic edema of the throat occurs epinephrine should be administered first Some patients respond well to aspirin but one must be reasonably certain that there is not also an allergy to this drug Calcium gluconate intravenously is of benefit in some instances and may be given daily ACTH or cortisone should be used essentially only in those instances of drug reactions where the symptoms are severe or alarming and do not respond to antihistamine therapy These hormones will usually clear up most of the active symptoms in a day or two However they do not shorten the course of the disease since the symptoms will recur if the administration of these agents is discontinued too early

Local and Nonspecific Therapy Local applications which may be beneficial are diluted vinegar calamine lotion and lotions containing small amounts of phenol When the lesions are superficial and the skin is red creams or ointments containing antihistaminic drugs may be helpful

In the presence of chronic urticaria when the cause was not identified various forms of nonspecific therapy have been tried with uncertain results Among these were injections of colon bacilli or typhoid vaccines autohemotherapy, fever therapy, histamine azoprotein and histamine injections In general it may be said that the treatment of these chronic unclassified cases is unsatisfactory Remissions occur rather frequently but there usually are no satisfactory explanations for them

ATOPIC DERMATITIS (FLEXURAL ECZEMA)

This should be regarded as a true allergic manifestation the allergen usually reaching the skin from the blood This is in contrast to the direct contact of the allergen with the skin as occurs in contact dermatitis The disease is atopic that is it is associated with other allergic manifestations such as hay fever and asthma in the patient and in the family, and characteristically is manifested by immediate whealing skin tests and transferable sensitizing antibodies It is a lichenifying dermatitis occurring predominantly on the face folds of neck, flexures of elbows and popliteal spaces It occurs chiefly in infants most of whom experience a spontaneous and permanent disappearance of the lesions A small percentage persist to childhood and a still smaller group continue with a chronic form of the disease into adult life

In infants and younger children when an allergic factor can be localized it is usually a food most commonly milk wheat, or egg In older children and adults inhalants constitute important allergenic causes Among the most important of these are house dust feathers pollen and molds In most instances elimination procedures are indicated during treatment In some hypodermic desensitization with inhalant allergens are necessary In such instances a conservative schedule should be employed

posed to high heat and humidity, particularly if the exposure continues over a period of days This is especially true of people moving to unaccustomed climates Anorexia, sweating weakness faintness headache, nausea vomiting and oliguria or other signs of dehydration may be present This syndrome is largely a matter of physical depletion from the effects of heat and the temperature regulating mechanisms of the body are not seriously disturbed as is indicated by little elevation of temperature

Treatment

Rest (if possible in a cool location) fanning salinized water (0 1 per cent sodium chloride) given orally mild sedation and general supportive measures usually prove recuperative If fluids taken orally are not retained, their loss may be supplemented by isotonic solution of sodium chloride given intravenously If symptoms of shock are present they should be combated by intravenous injections of plasma in addition to the isotonic sodium chloride In patients showing a rise of rectal temperature above 102° F sponging the body with cool water is advisable This condition demands careful observation to determine whether there are signs of heat stroke which requires much more energetic treatment

HEAT STROKE

Heat stroke (hyperthermia) is a medical emergency Prognosis depends on the promptness and vigor with which treatment is instituted Persons engaged in strenuous exertion in hot humid climates are often subject to heat stroke Failure to become acclimated predisposes to heat illness Under these conditions an excessively heavy load is thrown upon the heat regulating mechanisms of the body which fail allowing temperatures to rise to dangerous levels When air temperature rises above body temperature heat dissipation from the body depends largely upon the cooling effect produced by the evaporation of perspiration In heat stroke sweating characteristically ceases, and the skin becomes hot and dry People who have been subjected to extensive sympathectomy are apt to be unusually susceptible to heat stroke because they are unable to perspire freely Drugs which suppress sweating may exert a similar influence

Although there may be premonitory signs of weakness malaise nausea and confusion the symptoms usually develop suddenly, the patient becoming unconscious often delirious with rectal temperatures of 106–110° F Convulsions may occur and there is grave danger of circulatory collapse The appearance of purpuric lesions of the skin has been reported in some cases Most of the symptoms express injury to the central nervous system resulting from exposure to excessively high temperatures and the chief objective of treatment is to lower the body temperature as expeditiously as possible In fatal cases hemorrhages and degenerative lesions in the brain heart and other organs are found There also is the distinct possibility of permanent injury to the central nervous system with consequent neurologic manifestations

The patient should be sprayed or sponged with cool water every five minutes and an electric fan should be used to encourage evaporation and cooling Ice water enemas may be used but this treatment is extreme and makes determination of the rectal temperature difficult Ice packs may be necessary The rectal temperature should be taken every ten or fifteen minutes the above measures being continued until the temperature reaches 102–103° F At this stage temperature readings may be taken less frequently but one must be on the alert for a secondary rise which occurs occasionally If such relapse takes place cooling measures must be reinstituted

Plasma should be given in amounts

25. Diseases of Physical Origin

JAMES PAISLEY HENDRIX

MAN is limited to a rather narrow range of change in physical environment unless he is aided by compensating and protective devices Exposure to variations in tempera-ture and barometric pressure much beyo the normal range are likely to cause him suffer severe discomfort which may culm nate in pathologic conditions

Exposure to Heat

ASIDE from actual burns or allergy in jury resulting from exposure to excessive heat may be classified symptomatically as (1) heat cramps (2) heat exhaustion and (3) heat stroke

HEAT CRAMPS

As the term implies heat cramps are in voluntary painful contractions of skeletal muscles especially those in the abdominal wall and the extremities They are precip-itated by excessive loss of sodium chloride (and possibly other substances) from the body during profuse perspiration Although the condition is painful it is rarely danger-ous unless associated with one of the other and more serious forms of heat illness

Treatment

The best treatment is prevention It is common practice for example for people subject to profuse perspiration caused by working in overheated surroundings to take 4–8 Gm of sodium chloride each day in tablet form preferably after meals in addi-tion to the liberal use of salt in the diet. Another convenient means of supplying ex-tra salt is to add it to drinking water in concentrations of 0 1–0 5 Gm per 100 cc according to tolerance If the solution is chilled its taste is not disagreeable at these concentrations

It may relieve the sufferer from heat cramps to remove him to a cooler place The oral administration of sodium chloride or the intravenous use of physiologic saline may give relief in cases manifesting severe symptoms

HEAT EXHAUSTION

Heat exhaustion covers a wide variety of symptoms likely to develop in people ex-

Changes in Barometric Pressure

HIGH ALTITUDE

With ascent to high altitudes the partial pressure of oxygen in the air decreases (although the percentage remains the same) the supply becoming inadequate for normal body needs People vary greatly in their susceptibility to altitude but symptoms of hypoxia may appear at 8000–10 000 feet and are almost always evident at 15 000 feet Exertion of course increases the susceptibility to symptoms The manifestations of hypoxia may appear gradually and insidiously so that the individual is not aware of his difficulty until he is in dangerous condition and unable to help himself Lethargy, interference with coordination dyspnea, confusion nausea and unconsciousness may occur, dependent upon the degree of oxygen deficiency

OXYGEN INHALATION

The *inhalation* of oxygen preferably from a mask, will relieve the symptoms except in altitudes so high that even 100 per cent oxygen becomes inadequate because it is under too low a pressure In general oxygen should be used by all inexperienced persons during air travel at altitudes above 10 000 feet, unless the aircraft is provided with a pressurized cabin designed to maintain a safe air pressure The commercial air lines make adequate provision for the protection of passengers from hypoxia

High altitude also may produce symptoms due to expansion of air in the internal ear and the sinuses and of gas in the bowel Rapid descent from high altitude may cause discomfort in the ears and sinuses if there is interference with ventilation of these cavities When return to low altitude is made, air must again enter the sinuses and ears to restore the pressure there to the atmospheric level The use of a nasal vasoconstrictor, such as the ' benzedrex inhaler or neo-synephrine solution, 0 25 per cent in isotonic solution of sodium chloride, may be necessary in such cases Simple maneuvers such as chewing gum swallowing with the nose closed and attempting to exhale with the mouth and nose closed, may relieve the symptoms

DECOMPRESSION SICKNESS

Decompression sickness may be encountered at high altitudes (above 30 000 feet) The same condition known as caisson sickness or bends has been observed for years in persons working under pressure greater than atmospheric if they are brought out too rapidly from the high pressure area In either case as a result of high altitude or of too rapid release from positive pressure nitrogen dissolved in the blood and tissues is released by the reduction in pressure and forms bubbles *which may act as emboli* or foreign bodies in the tissues The most frequent symptom is pain in the joints Abdominal discomfort choking sensations itching and various neurologic symptoms may result

Treatment

Once the condition has developed the only effective treatment is to return the individual to the higher pressure from which *he came In caisson disease, gradual decom*pression which allows time for elimination of excessive amounts of nitrogen, will prevent the symptoms

The most effective management of decompression sickness caused by high altitude is prophylaxis by inhalation of 100 per cent oxygen for at least forty five minutes (preferably longer) before beginning the flight The oxygen displaces much of the dissolved nitrogen in the body and thus prevents the

... to prevent or treat shock. The administration of oxygen is advisable, because of the extremely high metabolic rate caused by the hyperthermia.

When the temperature declines the vigorous treatment is gradually modified, isotonic solution of sodium chloride is administered, and sedatives may be used cautiously if they are needed to encourage rest.

Excessive cooling must not be induced. patient should be kept in bed and prote from the heat for several days and he sho be warned not to expose himself to h before normal sweating occurs. Further, must be made to realize that individu who have suffered heat stroke may rema unusually susceptible to heat and, cons quently must be cautious about exposure

Exposure to Cold

INJURY due to exposure to cold usually is in the form of frostbite with damage to peripheral parts of the extremities in which vasoconstriction is most complete. However immersion in cold water results in rapidly cooling the whole body to dangerous levels (hypothermia) which may result in death from heart failure.

FROSTBITE

Frostbite results from exposure to freezing or near freezing temperatures and usually involves the fingers and toes which are apt to be less well protected than the rest of the body and also are subject to considerable vasoconstriction when so exposed. *Trench foot* or immersion foot is a similar condition resulting from standing in cold mud or water. The temperature need not be so low to produce this condition probably because moisture destroys the insulating value of footwear. Treatment is lescribed in Chapter 11, Diseases of the rteries and Arterioles.

YPOTHERMIA

Hypothermia is usually caused by immer n in cold water. It should be treated by mpt warming because unless this is done y temperature will continue to fall after victim is removed from the cold en ment and death may result. Here the problem is to restore body heat before the heart fails.

In mild cases the subject should be wrapped in warm blankets and hot water bottles should be applied. In more severe cases the body should be immersed in a hot bath prior to wrapping in blankets. In the notorious Dachau experiments on immersion hypothermia with human subjects immersion in a hot bath at 104–122° F for ten minutes followed by application of warm wrappings was reported to be the most effective treatment. Pending confirmation of these results it would seem advisable that the bath not greatly exceed 104° F unless the exposure has been very severe.

Hot beverages and mild stimulants such as tea and coffee may be given when the patient is conscious but epinephrine is believed to be contraindicated because a tendency to cardiac irritability is usually manifested. Other drugs were found to be of little value in the experiments mentioned above. Auricular fibrillation is the rule with severe hypothermia. Frequent temperature readings should be taken and if body temperature does not rise additional warming will be necessary. If shock is present, it must be treated by usual methods but care should be exercised not to overload the heart while body temperature still is low.

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formation of bubbles of the gas when pressure is reduced

More rapid decompression of caisson workers is also made possible by the inhalation of pure oxygen before the decompression is begun

Noxious Gases

INJURY from exposure to gases may occur in several ways In general however the commonly encountered gases may be divided into two types those which cause irritation of the respiratory tract and those which produce asphyxia

IRRITATING GASES

Irritating gases vary in the degree and type of injury produced Thus a highly irritating substance such as ammonia fumes, produces coughing sneezing inflammation of the upper respiratory passages spasm and edema of the larynx On the other hand pulmonary irritants such as the war gas phosgene and nitrogen dioxide (nitrous fumes) may be inhaled in dangerous concentration without immediate irritation However these substances produce severe delayed irritation injury of the alveolar membranes and the formation of pulmonary edema Other gases such as chlorine and sulfur dioxide are apt to produce injury to both the upper and lower respiratory tract.

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If damage to the lungs is severe there may be serious derangement of the circulation because of congestion and edema in the lungs and consequent strain upon the right heart and distention of neck veins If the latter symptom is pronounced bleeding may be advisable but this must be done with caution because of the coexisting danger of shock due to loss of fluid into the lungs In fact if shock occurs administration of plasma may be necessary Again caution is necessary to avoid overloading the heart If the chief difficulty is in the lungs and there are no signs of shock the slow intravenous injection of 0 25–0 5 Gm of aminophylline may be of benefit

Death may occur from pulmonary edema shock and heart failure The patient should be under constant observation because delayed collapse may occur Absolute bed rest is imperative to decrease the demand for oxygen and the load upon the heart The cautious use of sedatives (no morphine or strong opiates) may be necessary to keep the patient quiet Small doses of codeine may be used for cough but depression of the respiratory center must be avoided Because of the danger of pneumonia the prophylactic use of penicillin or other antibiotics is advisable

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ASPHYXIATING GASES

Asphyxiating gases may produce their effects simply by the exclusion of oxygen as in the inhalation of nitrogen and methane in mine gases, or by a systemic toxic effect as in the inhalation of carbon monoxide, cyanide gas, and hydrogen sulfide *

In case of asphyxia from an inert gas, the only treatment necessary is the establishment and maintenance of adequate respiration and oxygen intake This should be accomplished by artificial respiration, if necessary, and inhalation of oxygen during the early stages of resuscitation Artificial respiration may be administered by the prone pressure method, by the tilting method, by intermittent pressure on a rebreathing bag attached to an oxygen mask by a respirator or by one of the automatic devices for giving oxygen by intermittent positive pressure breathing † In any form of artificial respiration, one must be sure that there is no respiratory obstruction and that an adequate airway is open

It must be realized that the brain is particularly vulnerable to oxygen lack and every effort should be made to shorten the period of oxygen deficiency as much as possible One also must take into account that the respiratory center may be seriously depressed by oxygen lack and when so depressed, may not respond to the drugs commonly used as respiratory stimulants Reliance should be placed upon adequate ventilation of the lungs with air or oxygen and not upon drugs

If the blood pressure is seriously depressed a circulatory stimulant to insure the delivery of oxygen from the lungs to the brain may be indicated Ephedrine 10 mg to 15 mg or neo synephrine 0 5–2 mg (0 05–0 2 cc of the 1 per cent solution) may be injected slowly into the vein to overcome hypotension in an emergency The blood pressure and heart action should be followed carefully during such injection If the need is less acute, the drugs may be given intramuscularly in two or three times the above dosage

* See also Chapter 50

† A relatively simple device of the latter type is the Pneophore manufactured by the Mine Safety Appliances Company Pittsburgh Pennsylvania

Carbon Monoxide

Of the gases which produce systemic poisoning carbon monoxide is most commonly encountered in accidental and suicidal poisoning It is the toxic agent of illuminating gas coal gases and exhaust gases from gasoline engines Carbon monoxide is essentially an inert gas, except for its great affinity for hemoglobin This results in the conversion of oxyhemoglobin to carbon monoxide hemoglobin with consequent decrease in the oxygen-carrying capacity of the blood However, this reaction is reversible and oxygen may displace carbon monoxide by mass action Increasing the carbon dioxide in the blood, thus lowering its *p*H, also aids in removal of carbon monoxide from hemoglobin Hence, 4–7 per cent carbon dioxide in oxygen should be given by inhalation as early treatment for carbon monoxide poisoning The carbon dioxide also helps to stimulate the respiratory center and increases oxygen intake Artificial respiration should be used if necessary

Carbon monoxide has an affinity for hemoglobin about three hundred times as great as that of oxygen Hence, even small concentrations may prove dangerous if inhaled for long periods The symptoms of poisoning are very insidious and the victim may become unconscious without being aware of his danger The lips usually turn cherry red because of the bright red color of carbon monoxide hemoglobin

Cyanide

Cyanide gas produces asphyxia by inactivating oxidative enzymes in the cells of the body tissues and thus causes true cellular asphyxia The gas is so toxic that death

formation of bubbles of the gas when pressure is reduced

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Treatment

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However, if the skin is wet or its resistance is lowered by other means, there is apt to be less burning. If respiration or circulation are seriously disturbed, there may be secondary damage to the brain from lack of oxygen, even though the patient survives.

TREATMENT

Treatment of serious electric shock should be immediate, and should be continued until the victim recovers or until rigor mortis begins. The matter of first importance is to break the contact of the victim with the source of current. Rescuers must use extreme caution, and body contact, either directly or through a conductor of electricity, must be avoided. A loose wire may be removed with a dry broom, stick or rope. Heavy rubber gloves or similar insulating material should be used to protect the rescuer if it is necessary to pull the victim away from his contact. It must be kept in mind that a high voltage current has sufficient force to penetrate light insulating materials.

Respiratory paralysis is not as dangerous as ventricular fibrillation. If the victim is not breathing he should be treated by artificial respiration at once, with supplementary use of oxygen if possible (see the discussion on asphyxiating gases). If the heart is beating and if adequate respiration is established, cardiac stimulants may not be necessary, but if cardiac contractions can not be heard or felt, their absen dicate ventricular fibrillation. Th of this condition will cause death minutes if more effective contract more adequate circulation are not The higher centers of the brain can only a few minutes after cessation c lation. If apparatus for administe brief countershock over the heart is a it may be used in an attempt to st fibrillation and permit resumption o mal contractions. Injection of 30–70 m procaine (1.5–3.5 cc. of a 2 per cent tion) into the heart may be effective in s ping ventricular fibrillation, but epine rine should not be used because it tends produce this condition.

If facilities are available, opening the a domen or chest to permit cardiac massag is fully justified in the attempt to save life. Such massage, if the heart can be grasped in the hand, will sustain some circulation of the blood while other measures are tried in the attempt to restore heart action. Artificial ventilation of the lungs, of course, must be carried out simultaneously. As long as circulation can be supported artificial respiration should be continued.

If the victim survives, rest in bed for several days is imperative until the extent of any secondary effects of anoxia can be determined.

Motion Sickness

ILLNESS due to unaccustomed movement of the body in space may be precipitated in many ways. It usually is associated with avel as is the case in seasickness with hich voyagers have been afflicted since ne immemorial. In more recent times, vel in trains, automobiles, and airplanes quently produces motion sickness in susceptible individuals. Swinging and riding on amusement devices such as the merry go round also may cause symptoms.

The mechanism of motion sickness is not well understood despite investigations during the second World War. It has been generally supposed that disturbance of vestibular function is a pr

follows rapidly after its inhalation in lethal amounts A brief respiratory stimulation caused by the action of cyanide on chemo receptors of the carotid body only increases the intake of gas and hastens death Cyanide gas is used in gas chambers for capital punishment

Because of its rapid action opportunities to treat cyanide poisoning are rare When the drug is ingested as a salt its action is somewhat slower, but is still too rapid to be combated effectively in most cases Cyanide in the body will combine with methemoglobin to form relatively nontoxic cyan methemoglobin Hence in treatment of cyanide poisoning an attempt is made to form methemoglobin quickly by the inhalation of amyl nitrite and the intravenous injection of sodium nitrite Ten cc of a 3 per cent solution of sodium nitrite should be injected in two to four minutes followed by 50 cc of 25 per cent solution of sodium thiosulfate The latter substance converts cyanide to thiocyanate If the solutions are not at hand, amyl nitrite should be administered while they are being prepared the fall in blood pressure from the nitr is too great 10–30 mg of ephedrine injected intramuscularly, may be advisable excessive amounts of methemoglobin are formed oxygen therapy or transfusions may be necessary The patient should be kept under careful observation because the symptoms may recur

In asphyxiation caused by exposure to smoke and fumes the victim may encounter a mixture of asphyxiating irritating and toxic gases Carbon monoxide is commonly present in smoke Treatment must be based upon the symptoms and careful diagnosis Of course the matter of greatest importance is to establish adequate ventilation of the lungs and to be sure that oxygen is delivered to the tissues particularly the brain, as quickly as possible •

• Many other dangerous gases may be encountered in particular situations in industry The reader is referred to standard works on industrial medicine and toxic gases

Electric Shock

EXPOSURE to the injurious effects of electric current is a common hazard in the home, in industry and in accidents involving falling wires or unexpected contact with transmission lines So many factors govern the degree of injury that exposure to relatively low voltage may be dangerous on occasions whereas an individual may survive contact with a high tension circuit contact with an electrical circuit while a part of the body is in contact with a good grounding device such as a bath tub water pipes or steel building is particularly hazardous

In passing through the body an electric current will choose the shortest path from point of entry to contact of exit If there are multiple body contacts, several pathways will be followed This is of importance in understanding the effects of the current If the brain is in the path of the current it may be seriously injured and convulsions coma or respiratory paralysis may follow The heart is particularly vulnerable because its contractions will be altered by electric current Ventricular fibrillation or abrupt cardiac arrest may be produced from short contact An additional hazard from more prolonged contact is tetanic contraction of respiratory muscles and consequent asphyxiation The resistance of the skin is higher than the other tissues of the body (except bone) hence, burns of the skin are apt to occur at points of contact

26. Arthritis

IRVING E. STECK

DIFFERENT types of arthritis have differ ent etiologic factors, therefore, wherever possible, the causative agent should be established and upon this basis treatment instituted A given drug may be helpful in one arthritic condition and deleterious in another Aside from the harmful effects of improper treatment, one may lose valu time if the cause of the disease is o looked For example, treating a patient arthritis even with an innocuous dr when he has a malignant condition, m contribute to the hopelessness of the disea through the loss of time

Classification and Diagnosis

AN UNDERSTANDING of the various types of arthritis and the diseases with which arthritis and arthralgia may be asso ciated is therefore very helpful The follow ing classification is approved by the American Rheumatism Association

1 Arthritis due to specific infection
2 Arthritis due to rheumatic fever
3 Arthritis rheumatoid
4 Degenerative joint disease
5 Arthritis due to direct trauma
6 Arthritis due to gout
7 Neurogenic arthropathy
8 Neoplasms of joints
9 Hydrarthrosis, intermittent
10 Periarticular fibrositis
11 Diseases in which arthritis, arthralgia, or arthropathy are frequently asso ciated
 a Acromegaly
 b Acute disseminated lupus erythematosus
 c. Cyst of meniscus of knee
 d Dermatomyositis
 e Drug intoxication
 f Erythema multiforme exudativum
 g Erythema nodosum
 h Hemophilia
 i Hysteria
 j Ochronosis
 k Osteochondritis dissecans
 l Osteochondromatosis
 m Periarteritis nodosa
 n Psoriasis
 o Pulmonary osteoarthropathy
 p Purpura, various types
 q Raynaud's disease
 r Reiter s disease
 s Scleroderma
 t Serum sickness

other influences such as visual kinesthetic and psychologic factors must be taken into account Disagreeable sights and odors especially are apt to aggravate the illness Probably 80 per cent of the population is susceptible to motion sickness under severe conditions but the susceptibility varies greatly among individuals

Most persons who experience motion sickness will become adjusted and lose their symptoms after several days on a sea voyage In air travel the trip seldom lasts long enough to permit the development of tolerance The symptoms of motion sickness are too well known to require comment however it must be recognized that severe nausea and vomiting long continued may result in serious dehydration and acidosis which may require the parenteral administration of fluids

Many remedies and devices have been recommended for the treatment of motion sickness but most of the traditional ones are of little or no value Many mixtures of drugs have been advised the chief component of most being one or more of the belladonna alkaloids However it appears that hyoscine (scopolamine) alone is as effective as the mixtures The usual dose is 0 6 mg of the hydrobromide one hour before exposure repeated three or four times daily as required and tolerated Dryness of the mouth and paralysis of visual ccommodation may be troublesome side ffects Benzedrine sulfate 5 10 mg may be used to counteract excessive sedat effects of the drug The use of barbitura is justified when sedation is needed to ov come important psychologic factors

Dramamine"

Apparently even more successful thar hyoscine in the prophylaxis and treatment of motion sickness is a new drug dramamine* which has been effective in a high percentage of cases It is given in doses of 50–100 mg by mouth one hour before exposure for prophylaxis and repeated as necessary three or four times daily Some individuals get adequate relief from half this dose If severe nausea is present and oral medication is impossible the drug may be given by rectum The tablet should be crushed and suspended in 30–60 cc of water or isotonic solution of sodium chloride to facilitate rectal administration

The side-effects of dramamine are minimal and are less apt to cause discomfort than those associated with hyoscine The mechanism of action of the drug in the relief of motion sickness is unknown at this time but apparently is not related to its antihistamine effect Some other antihistamine drugs also may protect against motion sickness because drugs of this group are apt to produce important effects upon the central nervous system

* 2 (Benzohydryloxy) N N d methylethylamine 8 chlorotheophyllinate

Arthritis Due to Specific Infections

GONORRHEAL ARTHRITIS*

Gonorrheal arthritis is an infectious articular disturbance secondary to genitourinary gonococcic infections It may be either acute or chronic Before sulfonamides and penicillin were available the disease occurred in 1–5 per cent of gonorrheal urethritis At present the incidence has dropped to 0 1–0 3 per cent this fall being directly attributable to the effectiveness of chemotherapy and antibiotic therapy

Diagnosis

Gonorrheal arthritis is characterized *anatomically* by the involvement of the articular or periarticular structures There is synovial thickening polymorphonuclear leukocytic, lymphocytic and macrophagic infiltration. In more severe cases there may be fibroblast formation with resultant synovial fibrosis

It is characterized *clinically* by a sudden onset of an acute polyarthritis or arthralgia involving in order of frequency the knees ankles feet wrists fingers and shoulders These joints may be painful swollen red hot, and tender Frequently there is limited motion The temperature is elevated to 100°–104° F

Laboratory examination reveals a rapid edimentation rate and leukocytosis Urehral smear shows gram negative diplococci nd the synovial fluid may reveal gonococci ther on direct smear or on culture The mplement fixation test of the blood and novial fluid for gonorrhea is positive in per cent of the cases three or four weeks r the onset of the infection This test ld be repeated three times at weekly vals to be considered conclusive A tive test does not necessarily rule out nfection On the other hand 10 per cent of the cases may be falsely po

A diagnosis of gonorrheal arthri justified if there is a history of r gonorrheal infection, if there is evid of gonorrheal urethritis if there are g cocci in the synovial fluid, or if the c plement fixation test of the blood synovial fluid is positive

Treatment

Penicillin has been found to be specific Failure to respond to penicillin should lead one to question the accuracy of the diagnosis, for example, the acute gonorrhea may have precipitated an exacerbation of an old rheumatoid arthritis or gonorrhea and rheumatoid arthritis may exist simultaneously Success of treatment depends on early recognition of the disease and immediate treatment with penicillin or with penicillin and a sulfonamide Inadequate treatment or delay may lead to serious damage of the affected structures A therapeutic trial with penicillin is justified if the diagnosis is in doubt

Dosage *Crystalline procaine penicillin G* should be given intramuscularly in doses of 300 000 units every twelve hours night and day for a period of seven to ten days If no improvement is noted within three or four days 20 000 units of penicillin in 10 cc of isotonic sodium chloride solution should be injected into the involved joint daily for a period of three days in addition to the intramuscular dose

Sulfonamides can be used effectively in those patients who cannot tolerate penicillin Sulfadiazine is the drug of choice and should be administered orally in doses of 1 Gm every four hours night and day for five days The dose should then be reduced to 0 5 Gm every four hours for the next ten days To prevent renal complica

also Chapter 40

DIAGNOSIS

The various types of joint disease have sufficient individual characteristics to enable one to make a correct diagnosis in most instances before therapeutic procedures are instituted Generally speaking a careful history and physical examination should offer a clue to the correct diagnosis For example gout is an uncommon disease among women 98 per cent of all cases occur in men On the other hand rheumatoid arthritis is most common among women, but rheumatoid spondylitis is predominant in men Hypertrophic arthritis rarely causes symptoms before the age of 40 Rheumatic fever generally occurs before the age of 15 Occasionally the history of the patient's reaction to past treatment may suggest a lead to the diagnosis

Physical Examination Careful physical examination may reveal the type of arthritis or the condition producing the arthralgia The character of the swelling such as fusiform swelling of the fingers, swelling of the proximal interphalangeal joints or metacarpal phalangeal joints is characteristic of rheumatoid arthritis On the other hand swelling of the distal phalangeal joints with Heberden's nodes is diagnostic of hypertrophic arthritis The finding of tophi is peculiar to gout Subcutaneous nodules are suggestive of rheumatic fever Changes in pupillary or knee reflexes may be due to syphilis Raynaud's disease causing stiffness and pain in the fingers may simulate rheumatoid arthritis

Laboratory Tests A few simple laboratory tests will confirm the diagnosis in many instances and establish a sound basis for the therapeutic procedure The sedimentation rate is rapid in rheumatoid arthritis, rheumatic fever, and gonorrheal arthritis but normal in hypertrophic arthritis Blood uric acid is elevated in gout, however, an elevated blood uric acid does not necessarily indicate gout Complete blood examinations are useful in ruling out blood dyscrasias which may manifest themselves by articular disturbances Synovial fluid examination of swollen joints may reveal the etiologic agent An icterus index above 5 units is suggestive of traumatic arthritis due to hemarthrosis Smears of urethral discharge, prostatic secretions, vaginal and cervical discharge may aid in diagnosis

Roentgenology Roentgenologic examination of the affected parts will usually reveal the true nature of the pathologic process The roentgen ray findings of rheumatoid arthritis are typical There is periarticular soft tissue swelling local and generalized decalcification of bony trabeculae and progressive narrowing of the joint space In degenerative joint disease bony lipping may be seen at the joint margins Gout reveals punched out areas of bone most frequently seen in the great toe In suppurative arthritis there are circular zones of atrophy in the epiphysis In tuberculous arthritis there is marginal erosion of bone and destruction of the articular cortex No patient should be treated for arthritis unless a thorough roentgenologic examination of the affected part has been made

position by a *splint*, sandbags, or cast Ankylosis of the shoulder is not common When it cannot be prevented, the arm should be held in the above position The forearm should be maintained in slight supination

When the *hip joint* is involved, there is flexion, adduction, and internal rotation, with associated lordosis of the lumbar spine This may be prevented by keeping the hip *in extension The patient is kept on a firm* mattress with a pillow under the buttocks on the affected side When ankylosis is inevitable the legs should be kept extended and externally rotated at 5–10 degrees The hip should be flexed 15 degrees

The *jaw* is infrequently involved in gonorrheal arthritis Ankylosis may be prevented by the application of heat and frequent movement of the jaw which can be obtained by chewing gum Wedges of wood or cork maintained between the teeth but allowing an opening of at least one quarter of an inch will permit limited use of the jaw in the event of ankylosis

When splints are used, they should be removed once every *twenty four hours and* heat should be applied locally Heat, dry or moist, to the affected joint relieves pain, relaxes muscle spasm and induces hyperemia by dilating the blood vessels In the acute stage moist heat is more efficacious than dry heat This is best carried out with hot fomentations to the involved joints *When no splints are used,* hot packs should be applied four to six times daily for twenty minute periods

Massive effusions should be aspirated, thereby relieving pain and pressure in the articular structures Aspiration also decreases the tendency for adhesions to form, and minimizes the destruction of the cartilage

Analgesics, such as acetylsalicylic acid, 0 6 Gm, phenobarbital, 30 mg, and codeine 15–30 mg administered every four hours, are usually sufficient to keep the patient comfortable The patient should be kept in bed until the fever, swelling tenderness, pain, and all signs of inflammation have subsided

Physical Therapy*

Physical therapy is one of the most important phases of treatment and should not end with the subsidence of the acute phase of gonorrheal arthritis Rehabilitation of *the patient and restoration of the affected* joints to normal must be attempted. Heat, massage, and graduated exercises should be instituted In the subacute stages, *heat* in any form, which is most comfortable for the patient, may be used Included are hot fomentations, hot tub baths, whirlpool baths, contrast baths, infrared or ultraviolet light, electric pad or hot water bag

Massage following the application of heat is indicated only when the acute phase of gonorrheal arthritis has subsided The affected joints should not be massaged as long as there is elevated systemic temperature, or as long as the affected part is inflamed, or when massage aggravates the pain, swelling, tenderness, and stiffness.

Physiologically, massage increases the venous and lymphatic return, blood flow and absorption are increased locally, and the tendency to adhesions and muscular atrophy is decreased

Massage must be individualized to the joint involved and to the condition of the patient In general, the massage should at first be gentle, of a stroking movement gradually increasing in intensity, such as *kneading and friction* The proximal part of the extremity should be massaged before the distal part For example, in gonorrheal arthritis of the knee, massage is begun at the knee and carried toward the hip and then from the ankle to the knee, and lastly, from the toes to the ankle This procedure allows the proximal lymph and venous channels to open and drain

* See also Chapter 45

tions such as hematuria and anuria, the urine should be kept alkaline by administering 12–16 Gm sodium bicarbonate daily in divided doses Sulfadiazine is more soluble in alkaline than in acid urine and this reduces the likelihood of precipitation of crystals in the tubules and pelvis of the kidney Fluids sufficient to insure 1000–1500 cc of urinary output in twenty four hours should be given

Prevention of Deformity

While penicillin and the sulfonamides are the drugs of choice in the treatment of gonorrheal arthritis additional measures are of benefit Rest in bed during the acute phase is vital since active motion increases pain and may damage the articular structures The affected joints should be supported with splints or with posterior molded casts and padded with cotton Pressure points should be avoided and splints held in place with gauze elastic bandages, or adhesive tape The splints should be maintained during the acute phase but the joint should be manipulated to prevent adhesions from forming

Ankylosis There is a marked tendency in gonorrheal arthritis for articular adhesions to form The resultant ankylosis may be prevented by gentle passive exercise of the joint through a full range of painless motion In spite of these precautions ankylosis may develop in the more severe cases The splints therefore should be applied to the affected parts so as to prevent deformity If ankylosis is inevitable the joint should be put in the position of optimum function

The *knees* commonly ankylose in flexion external rotation and subluxation This deformity is usually due to the position which the patient assumes in bed To minimize the pain in the joint, the knee is flexed to lessen the strain on the hamstring muscles and relax the capsule With continued flexion the hamstring muscles be-

come shorter and subluxation of
ensues This deformity can be p
by prohibiting the use of pillows u
affected knees and by the use of a p
splint which should extend from the
thigh to the toes When ankylosis
minent the knee should be placed in f
of 5–10 degrees for optimum positio
weight bearing

When the *ankle* and *foot* are invo
the most common deformity is foot
and valgus This is due to the musc
spasm and contraction of the gastrocnem
muscle Foot drop can be prevented
eliminating the pressure of the sheets a
covers on the toes and foot, by using
cradle over the feet and placing the cove
over the cradle To further minimize th
possibility of foot drop, the foot should b
placed in a posterior molded splint and
kept at right angles to the leg and in
slight pronation When foot drop is in
evitable the foot should be placed in slight
plantar flexion and slight pronation

The *wrist* frequently ankyloses in palmar flexion This can be avoided by keeping the wrist in a cock up splint but giving daily exercises When ankylosis cannot be prevented the wrists should be placed in dorsiflexion of 25–30 degrees with the fingers semiflexed and the thumb in neutral position

The *elbow* ankyloses in flexion with a loss of the carrying angle This can be prevented by alternating splinting and exercise When ankylosis is imminent the elbow should be placed at 90–100 degrees of flexion with forearm held midway between supination and pronation

The *shoulder* usually ankyloses in adduction and internal rotation To prevent this deformity the patient should be kept on a firm mattress to minimize muscle spasm and drooping of the affected shoulder The arm should be kept in adduction at approximately 70 degrees with 30 degrees forward flexion It may be held

pressure on the articular structures Tapping the joint also decreases the tendency for adhesions to form and minimizes the destruction of cartilage This procedure may be repeated as effusions reappear

Analgesics, such as acetylsalicylic acid 0 6 Gm, phenobarbital, 30 mg, and codeine 15–30 mg administered every four hours are usually sufficient to keep the patient free from pain

Like gonorrheal arthritis the patient with pneumococcal arthritis should be kept in bed until the systemic fever, swelling tenderness pain and all signs of inflammation of the involved joints have subsided Details of general management are similar to those for gonorrheal arthritis

SYPHILITIC ARTHRITIS*

Syphilitic arthritis is an articular disturbance, secondary to a syphilitic infection and caused by *Treponema pallidum* It may occur as a manifestation of congenital syphilis, being found in 5 per cent of children with this disease Articular involvement is less common in secondary and tertiary syphilis

Diagnosis

Syphilitic arthritis is characterized anatomically by vascular and perivascular cellular infiltration and fibrous proliferation resulting in periostitis Gummatous articular lesions lead to destruction of cartilage, synovial membrane proliferation and pannus formation

In the congenital form there may be osteochondritis symmetrical serous synovitis or gummatous synovitis In the secondary stage the pathologic changes may be synovitis, tenosynovitis and bursitis In the tertiary stage there may be gummatous lesions involving the synovial membrane and capsule There may be decalcification of bone with marginal lipping and massive destruction of cartilage, as in Charcot joints

Clinically the congenital form is characterized by osteochondritis (Parrot s pseudoparalysis) frequently found in the first weeks of life Periarticular swelling epiphyseal separation, or fracture commonly affects the upper extremities Symmetrical serous synovitis (Clutton s joints) is a painless swelling of the knees usually found in congenital syphilitics between 8 and 16 years of age

In secondary syphilis, the symptoms may be those of arthralgia or arthritis of the large joints Pain is characteristically more severe at night because of involvement of the periarticular structures periostitis or syphilitic osteomyelitis This pain is not relieved by rest There may be tenderness and swelling of the structures adjacent to the joint Limitation of motion is not uncommon

Articular lesions are more common in tertiary syphilis in the form of gummatous arthritis There is irregular swelling of the joint but no pain and no limitation of motion The Charcot joint is present in about 10 per cent of tabes dorsalis, usually involving the large joints The involved joint is painless swelling is marked and there is complete loss of anatomic outline Hypermobility and crepitation due to loose bodies are characteristic Associated signs and symptoms of tabes such as Argyll Robertson pupil absent knee jerks positive Romberg sign and loss of deep sensation are usually present

The roentgenographic findings of osteochondritis are decalcification epiphyseal irregularity periosteal thickening and widening of the joint space Roentgen ray examination of the Charcot joint shows massive destruction of all the articular structures

The *laboratory findings* may reveal a positive Wassermann test of the blood of the synovial fluid or of the spinal fluid A

* See also Chapter 39

Active therapeutic *exercises* should not be started until the affected areas are entirely free of pain while at rest No joint should be exercised to the point of exhaustion, or to the point of increased pain, swelling or stiffness The joint should not be forced during exercise as this may result in an acute exacerbation of symptoms

The exercises should be graduated, the aim being to restore the affected joints to normal function This is best carried out in the following steps Contraction of the muscles by the patient without movement of the joint, active exercises of the joints without weight bearing and graduated exercises with weight bearing The frequency of the exercises should be gradually increased from one to three times daily Not infrequently there is some pain following active exercise If this pain persists for longer than two or three hours, the therapeutic exercises should be discontinued, and resumed after several days of rest *

TUBERCULOUS ARTHRITIS†

Tuberculous arthritis is an infectious articular disturbance secondary to systemic tuberculosis It is usually chronic, gradual in onset, and associated with either pulmonary or genitourinary tuberculosis With the decrease in frequency of the bovine type of tuberculosis, because of the pasteurization of milk, there has been a corresponding decrease in the incidence of tuberculous arthritis The disease is now caused almost entirely by the human type of tubercle bacillus

Diagnosis

It is characterized *anatomically* by synovitis, destruction of cartilage, marginal erosion of bone, and the formation of granulation tissue, leading to fibrosis and fibrous ankylosis

It is characterized *clinically* by monoarticular pain, swelling, stiffness, and limitation of motion Atrophy of the adjacent tissues is a prominent feature Tuberculous arthritis may affect any joint, but the joints most commonly involved are the spine, hips, and knees The disease most commonly affects children and young adults

Useful procedures are roentgen ray study of the joint involved, biopsy of articular tissue or regional lymph nodes, and aspiration of joint effusions The roentgenograms may not be diagnostic or differentiate a tuberculous bony lesion from other arthritides, but they may show periarticular swelling, bony decalcification, or sclerosis, marginal proliferation, or destruction of bone and narrowing of the joint space Sequestra and cold abscesses may be found later in the disease

A definite diagnosis can be established if the regional lymph nodes or synovia show tuberculous lesions on biopsy If this is not conclusive, aspiration of the joint fluid may yield the organism, by direct smear or through guinea pig inoculation

Treatment

Streptomycin has been reported of value in the treatment of tuberculous arthritis, especially if treatment is instituted early Tuberculosis of the extremities is claimed to respond more favorably than lesions of the spine to this drug

Dosage Streptomycin should be given intramuscularly in 0 5 Gm doses every twelve hours, day and night for ninety to one hundred and twenty days Dihydrostreptomycin is less likely to cause toxic manifestations of vertigo, ataxia and albuminuria than streptomycin on a comparable dosage but may cause more frequent deafness When these occur the drug should be temporarily discontinued until symptoms abate In most instances patients will tolerate the drug after a rest period Signs of sensitization to the drug may manifest themselves in headache, pruritus, cutaneous

* For detailed exercises see end of this chapter
† See also Chapter 16

joints In the early stages rest in bed, aspiration of effusions to reduce the distention of the capsule, braces, and splints help to keep the patient comfortable* Surgical fusion is not successful due to the complete disorganization of the articular surfaces

BRUCELLAR ARTHRITIS†

Brucellar arthritis is an infectious articular disturbance caused by the Brucella micro-organism, more commonly *Brucella melitensis* and *Br suis* It may be either acute or chronic

The incidence of true arthritis in Brucellosis is rare, but arthralgia is common in over 50 per cent of the patients

Diagnosis

The disease is characterized *clinically* by severe pain of the sacroiliac joints or along the course of the sciatic nerve (sciatic neuritis) Arthralgia, myalgia neuralgia, and hydrarthrosis are common features Transitory pain tenderness, and swelling of the larger joints are not uncommon

The *laboratory findings* may reveal a positive blood synovial fluid, urine, or stool culture after ten days incubation The agglutination test is usually positive in the first week of the disease but may be entirely absent throughout the illness A titer of 1 80 or higher must be present to be significant The brucellergin skin test is less reliable than the agglutination test It should be used when the agglutination test is negative When the skin test is positive *the phagocytic index will determine* whether the positive skin reaction is due to an active or inactive brucellosis A positive phagocytic reaction is present in the immune or inactive brucellosis A negative phagocytic reaction in the presence of a positive skin test indicates activity of the disease

* See Gonorrheal Arthritis
† See also Chapter 6

Treatment

Aureomycin for *Br melitensis* or dihydrostreptomycin in combination with sulfadiazine for *Br abortus* are the drugs of choice in the treatment of joint lesions in brucellosis Aureomycin is an antibiotic that has been shown to possess antibrucellar activity The advantage of aureomycin over streptomycin lies in the fact that the former is less toxic and that it can be administered orally This feature makes it possible to administer the drug without hospitalizing the patient

Dosage

The dosage of aureomycin is as follows

Day	*Total dose*	*4 divided doses each every 6 hrs*
1 st	0 2 Gm	0 05 Gm
2nd	0 6 Gm	0 15 Gm
3rd	1 6 Gm	0 4 Gm
4th	2 0 Gm	0 5 Gm
5–15th	4 0 Gm	1 0 Gm

Dihydrostreptomycin is effective against the three species of Brucella *Br abortus, Br suis,* and *Br melitensis* This drug in combination with sulfadiazine is extremely effective against brucellosis The combination includes the administration of dihydrostreptomycin in 0 5 Gm doses every six hours, day and night, intramuscularly for fourteen days and of sulfadiazine orally every four hours for fourteen to twenty one days The drugs should be administered simultaneously The initial dose recommended is 3–4 Gm, followed by 1 Gm Sodium bicarbonate 12–16 Gm daily in divided doses should be given every twenty four hours to keep the urine alkaline and prevent renal complications such as hematuria and anuria Enough fluid to insure at least 1000–1500 cc of urinary output in twenty four hours should be given

Dihydrostreptomycin and the sulfonam

positive blood Wassermann and a negative synovial fluid test make a diagnosis of syphilitic arthritis dubious On the other hand, a positive synovial fluid Wassermann and a negative blood Wassermann are consonant with a diagnosis of syphilitic arthritis In case of doubt, an articular biopsy will confirm the diagnosis Finally, the response of the articular lesion to antisyphilitic treatment is significant

Treatment

The articular manifestations of congenital and secondary syphilis respond to antisyphilitic treatment The objective at this stage is eradication of the spirochetes promotion of healing and prevention of relapses This goal can best be achieved if the disease is congenital or in the secondary stage as response is less in the tertiary stage since too much damage has occurred in the articular structures Treatment is of no benefit in tabetic arthropathy

Drugs used in the treatment of syphilitic arthritis are penicillin trivalent arsenic and bismuth All of these drugs possess spirocheticidal activity

Penicillin is an active spirocheticide Its effectiveness in the treatment depends on the length of time of therapy, the maintenance of a constant level and the concentration of penicillin throughout the treatment period Arsenic is spirocheticidal and its therapeutic effect depends on the amount of arsenic to which the spirochetes are exposed Bismuth is a less powerful spirocheticidal agent than penicillin or arsenic Its value lies in the fact that it is absorbed and excreted slowly, thereby exerting a prolonged effect Lesions which are resistant to penicillin may respond to arseno bismuth management and conversely lesions resistant to arsenic or bismuth may respond to penicillin

Dosage An effective schedule for secondary and late congenital syphilitic arthritis provides a total dose of 6 000 000 units of *penicillin* administered within a period of ten days The drug is administered intramuscularly in doses of 600 000 units every twenty four hours for a total of 10 injections Crystalline procaine penicillin G in aqueous solution is superior to amorphous penicillin

It is unnecessary to fortify penicillin with arsenic and bismuth in the first course of treatment However, if the response to penicillin is not adequate a further course may include one or both metals As the arsenic portion of such a course, 0.48 Gm of oxophenarsine hydrochloride in 8 injections of 60 mg each daily, or every other day may be given A total of 1 Gm of bismuth subsalicylate, in 5 injections of 0 2 Gm each can be given every two days concurrently with penicillin

For early congenital syphilitic osteochondritis the total dose of crystalline procaine penicillin G is 100 000 to 400 000 units per kg body weight administered intramuscularly every twenty four hours in divided doses for eight to fifteen days

Complications of penicillin in the treatment of syphilitic arthritis include therapeutic shock or the Jarisch Herxheimer reaction This reaction is not peculiar to penicillin but is common to all forms of antispirocheticidal therapy The reaction occurs in 50 per cent of all patients being treated for syphilis with penicillin It is characterized by fever with or without exacerbation of the primary or secondary lesions within twelve hours of the start of treatment The shock may last from two to four hours The intensity of the reaction is proportional to the severity of the infection Thus in early syphilis the reaction may be mild but in late and congenital syphilis the reaction may prove disastrous since no effective counter measures exist

Penicillin and other antisyphilitic measures are of no value in tabetic arthropathy Treatment of Charcot joints depends largely on factors other than the involved

joints In the early stages rest in bed, aspiration of effusions to reduce the distention of the capsule, braces, and splints help to keep the patient comfortable * Surgical fusion is not successful due to the complete disorganization of the articular surfaces

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Dihydrostreptomycin and the sulfonam

ides are toxic drugs The unfavorable reaction therefore may be even greater, if these two drugs are used simultaneously No patient should be treated with this combination unless there is careful supervision in an institution Toxicity from dihydrostreptomycin, requires that the drug should be temporarily discontinued Hypersensitivity from the use of this drug may manifest itself in the form of headache transient paresthesia of the lip or gastrointestinal disturbances with nausea and vomiting These symptoms usually can be controlled by using antihistaminic drugs in doses of 50–100 mg three times daily

While aureomycin or dihydrostreptomycin in combination with a sulfonamide is effective in the treatment of brucellar arthritis *general measures* should not be neglected Rest in bed during the acute stage of the disease and for ten to fourteen days after the temperature has returned to normal and the tenderness swelling pain and all signs of inflammation of the involved joints have receded is essential To control restlessness and irritability phenobarbital 30 mg and to alleviate joint pains acetylsalicylic acid 0 6 Gm are administered every four hours

The rehabilitation of the involved joints may require the same attention as other acute infectious arthritides

MENINGOCOCCAL ARTHRITIS

Meningococcal arthritis is an acute infectious articular disturbance secondary to a meningococcic infection It is caused by a gram negative coccus the meningococcus It occurs in 5–20 per cent of meningococcal infections

Diagnosis

It is characterized *anatomically* by a seropurulent inflammation of the synovial membrane, the formation of granulation tissue, and the destruction of articular cartilage

The condition is characterized *clinically* by a sudden onset of transient polyarticular arthralgia or by a sudden onset of monoarticular pain tenderness and swelling The effusion is usually purulent, but serous effusion is not uncommon

Laboratory examination will usually show the organism in the smear or culture of the cerebral spinal fluid In one third of the cases the diplococcus will be found in smears or cultures of the synovial fluid

Treatment

Treatment should be started as soon as a diagnosis of meningococcal arthritis is made The drugs of choice are penicillin or a sulfonamide Sulfadiazine is the preferred sulfonamide

Dosage The initial oral dose of *sulfadiazine* is 4 Gm followed by 1 Gm every four hours day and night The drug should be continued for three to five days after all signs and symptoms of the articular lesion have disappeared The dose may be reduced if the blood level becomes higher than 15 mg per 100 cc It should be increased if the blood level is lower than 10 mg

In the presence of persistent vomiting sulfadiazine may be administered intravenously, in an initial dose of 5 Gm, as a 0 5 per cent solution of sodium sulfadiazine in sterile isotonic saline Thereafter 2 Gm as a 0 5 per cent solution should be given intravenously every eight hours The drug should be administered orally as soon as the patient can tolerate it

The urine should be kept alkaline by the administration of 12–15 Gm of sodium bicarbonate daily in divided doses In the presence of vomiting 500 cc of one-sixth molar sodium lactate should be used immediately following the intravenous administration of sulfadiazine

Penicillin alone may be used in meningococcal articular lesions when a sulfonamide is not tolerated or it may be administered simultaneously when the infection is overwhelming

Penicillin should be administered intramuscularly in an initial dose of 100 000 units and 50 000 units thereafter every three hours night and day *Crystalline procaine penicillin G* in aqueous solution is superior to amorphous penicillin If no improvement is noted within three or four days 20 000 units of penicillin in 10 cc of isotonic sodium chloride solution should be injected directly into the involved joint once daily in addition to the intramuscular administration of the antibiotic The drug should be continued at these doses until improvement of the articular lesion is evident then it may be reduced gradually

In addition to the sulfonamide and penicillin general and local measures of *proved value in the treatment of other* acute articular lesions should be carried out These include rest aspiration splinting physical therapy and analgesics as for other types of infectious arthritis

ACUTE SUPPURATIVE ARTHRITIS

Acute suppurative arthritis is an articular disturbance of primary origin as in penetrating wounds or secondary to a systemic infection It is commonly caused by *Staphylococcus aureus* or *Streptococcus hemolyticus*

Diagnosis

The condition is characterized *anatomically* by synovial thickening with proliferation and pannus formation There is destruction of the articular cartilage with infiltration of polymophonuclear leukocytic and lymphocytic cells When the causative organism is a streptococcus there is synovial thickening and proliferation Destruction of articular *cartilage results from* a staphylococcus invasion of the articular structures

It is characterized *clinically* by a sudden onset of monoarticular pain, swelling redness and limitation of motion of the involved joint with associated systemic fever chills, and sweats The condition is common in youth and usually attacks the large *joints*

The *laboratory findings* reveal the organism in the synovial fluid The cell count may be increased to 300 000 to 400 000 cells with 90 to 100 per cent being polymorphonuclear leukocytes The blood culture usually is positive and may reveal the causative organism Roentgenography will reveal signs of disease after ten to fourteen days decreased joint space is seen

Treatment

Success of treatment of suppurative arthritis depends on early diagnosis the *finding of the causative organism and the* prompt energetic treatment with penicillin a sulfonamide adequate drainage, and early motion to prevent adhesions and ankylosis

Aspiration of the affected joint is invaluable in establishing an early diagnosis and as a therapeutic procedure Effusions should not be allowed to accumulate in the joint Frequent aspirations should be performed, as the proteolytic enzymes present in the purulent effusion destroy the articular cartilage When aspiration *will not re*move a thick purulent effusion arthrotomy becomes mandatory

The drugs of choice in suppurative arthritis are penicillin and/or a sulfonamide, when the organism is a staphylococcus or a streptococcus (Suppurative arthritis due to a pneumococcus meningococcus or gonococcus organism is discussed under these headings)

Dosage Crystalline procaine *penicillin G* in aqueous solution should be adminis

ides are toxic drugs The unfavorable reaction therefore may be even greater, if these two drugs are used simultaneously No patient should be treated with this combination unless there is careful supervision in an institution Toxicity from dihydrostreptomycin requires that the drug should be temporarily discontinued Hypersensitivity from the use of this drug may manifest itself in the form of headache transient paresthesia of the lip, or gastrointestinal disturbances with nausea and vomiting These symptoms usually can be controlled by using antihistaminic drugs in doses of 50–100 mg three times daily

While aureomycin or dihydrostreptomycin *in combination with a sulfonamide* is effective in the treatment of brucellar arthritis *general measures* should not be neglected Rest in bed during the acute stage of the disease and for ten to fourteen days after the temperature has returned to normal and the tenderness swelling pain and all signs of inflammation of the involved joints have receded is essential To control restlessness and irritability phenobarbital 30 mg and to alleviate joint pains acetylsalicylic acid 0 6 Gm are administered every four hours

The rehabilitation of the involved joints may require the same attention as other acute infectious arthritides

MENINGOCOCCAL ARTHRITIS

Meningococcal arthritis is an acute infectious articular disturbance secondary to a meningococcic infection It is caused by a gram negative coccus the meningococcus It occurs in 5–20 per cent of meningococcal infections

Diagnosis

It is characterized *anatomically* by a seropurulent inflammation of the synovial membrane the formation of granulation tissue, and the destruction of articular cartilage

The condition is characterized *clinically* by a sudden onset of transient polyarticular arthralgia or by a sudden onset of monoarticular pain, tenderness and swelling The effusion is usually purulent, but serous effusion is not uncommon

Laboratory examination will usually show the organism in the smear or culture of the cerebral spinal fluid In one third of the cases the diplococcus will be found in *smears or cultures of the synovial fluid*

Treatment

Treatment should be started as soon as a diagnosis of meningococcal arthritis is made The drugs of choice are penicillin or a sulfonamide Sulfadiazine is the preferred sulfonamide

Dosage The initial oral dose of *sulfadiazine* is 4 Gm, followed by 1 Gm every four hours day and night The drug should be continued for three to five days after all signs and symptoms of the articular lesion have disappeared The dose may be reduced if the blood level becomes higher than 15 mg per 100 cc It should be increased if the blood level is lower than 10 mg

In the presence of persistent vomiting sulfadiazine may be administered intravenously in an initial dose of 5 Gm as a 0 5 per cent solution of sodium sulfadiazine in sterile isotonic saline Thereafter 2 Gm as a 0 5 per cent solution should be given intravenously every eight hours The drug should be administered orally as soon as the patient can tolerate it

The urine should be kept alkaline by the administration of 12–15 Gm of sodium bicarbonate daily in divided doses In the presence of vomiting 500 cc of one sixth molar sodium lactate should be used immediately following the intravenous administration of sulfadiazine

Treatment There is no specific drug for the treatment of coccidioidal arthritis The best results have been obtained with the following procedure

The patient should rest in bed until the systemic and local signs of the disease have subsided and the temperature, blood count, and sedimentation rate have returned to normal A high vitamin, high-caloric diet should be maintained

An initial dose of coccidioidin, 0 01 cc., in a dilution of identical strength with the one that gives the positive coccidioidin skin reaction, should be injected intramuscularly Subsequent injections are increased by 0 01 cc to the point of tolerance, which is about 0 3 cc The frequency and total number of injections depends on the progress and the tolerance of each patient to the vaccine

In the acute stage of coccidioidomycosis, the acute joint involvement frequently subsides The chronic granulomatous stage of coccidioidal arthritis tends to progress and the prognosis is poor When there is no evidence of clinical improvement and the lesion is confined to an extremity, amputation is indicated

Actinomycotic Arthritis

Actinomycotic arthritis is an articular disturbance secondary to systemic actinomycosis and caused by the genus *Actinomyces* Involvement of articular structure is rare The spine is most frequently involved There is abscess and sinus formation The purulent discharge reveals mycelial filaments and diphtheroidal fragments The gram positive sulfur granules' are present only in about one third of the cases

Treatment Treatment of actinomycotic arthritis is both surgical and medical The drugs of choice are sulfonamides and penicillin The sulfonamides have been reported to be effective in the treatment of *Actinomyces bovis* or *Nocardia* infections The recommended sulfonamide is *sulfadiazine* An initial dose of 4 Gm, followed by 1 Gm every four hours, given orally for four months or until the articular lesion subsides, is recommended

The urine should be kept alkaline to avoid precipitation of sulfa crystals The sulfonamide level should be kept at 10-15 mg per 100 cc. of blood *

Penicillin should be given concurrently with the sulfadiazine Crystalline penicillin G in aqueous solution 50,000 units every four hours should be administered intramuscularly for three or four months Larger doses, as much as 1,000,000 units per day, may be used when there is no favorable response to the smaller dosage

Surgical procedures should be carried out in order to provide adequate free drainage of the sinuses

Many advise the use of *potassium iodide* in a saturated solution concurrently with the sulfadiazine, and the penicillin in the belief that it promotes resolution, this is questionable An initial dose of 0 2 cc of saturated potassium iodide in 60 cc. of milk is given orally three times daily after meals This dose is increased daily by 0 062 cc until 1 2 cc is given three times daily The dose is then reduced to 0 2 cc and the original procedure is repeated The duration of treatment is four months or until the patient is well The treatment should be reinstituted when the symptoms recur

During the acute phase, rest in bed, and a high caloric and high vitamin diet are essential

Blastomycotic Arthritis

Blastomycotic arthritis is a chronic articular disturbance secondary to systemic blastomycosis and caused by *Blastomyces dermatitidis* It is characterized by the formation of granulation tissue of the periarticular and articular structures with abscess and sinus formation The organism

* See also the use of sulfadiazine in meningococcal arthritis

tered intramuscularly in doses of 300 000 units every twelve hours day and night Concurrently, 20 00 units of penicillin in 10 cc of isotonic sodium chloride solution is injected into the affected joint once daily The antibiotic is continued until improvement of the articular lesion is evident and then is reduced gradually

Sulfonamides can be used effectively when there is a poor response to penicillin and when the patient cannot tolerate penicillin The preparation recommended is sulfadiazine when used an initial oral dose of 4 Gm followed by 1 Gm every four hours day and night is recommended The drug should be continued for three to five days after all signs and symptoms of the articular lesion have disappeared The dose should be reduced if the blood level is higher than 15 mg per 100 cc of blood It should be increased when the sulfonamide blood level is lower than 10 mg

When a sulfonamide is administered sodium bicarbonate 12–16 Gm should be given daily in divided doses to keep the urine alkaline and reduce the precipitation of sulfonamide crystals in the tubules and pelvis of the kidneys Fluids sufficient to insure a urinary output of 1000–1500 cc every twenty four hours should be given

While the administration of penicillin and/or a sulfonamide and aspiration of the affected joints are specific measures in the treatment of suppurative arthritis additional measures to insure optimum results are imperative These include rest in bed during the acute phase splinting of affected joints passive motion heat to affected parts transfusion of whole blood as indicated analgesics to control pain high caloric high vitamin diet prevention of deformity massage and exercise in the recovery stage as in other forms of infectious arthritis

Surgery is indicated only when medical treatment fails to correct deformity and to obtain optimum function of the joints

MYCOCTIC DISEASES OF THE JOINTS

Coccidioidal Arthritis (Desert Rheumatism)

Coccidioidal arthritis is an acute or chronic articular disturbance secondary to coccidioidomycosis, and is caused by *Coccidioides immitis* Acute coccidioidal arthritis is reported to occur in one-third of the patients with coccidioidomycosis

Diagnosis The condition is characterized *anatomically* by a primary lesion in the lungs and secondary involvement of the articular and periarticular structures The organism is encircled by plasma cells giant cells and epithelial cells There is abscess formation and less frequently formation of granulomatous tissue

Coccidioidal arthritis is characterized *clinically* by a sudden onset of pain tenderness slight swelling and limitation of motion of a joint In this acute phase there is no effusion and no articular damage Coccidioidal granulation tissue in the articular and periarticular structures is a later development in a small number of cases

Significant *laboratory tests* are the isolation of the organism in the synovial fluid sputum or gastric contents, and biopsy of the affected joint The complement fixation test is important The titer of the complement fixation is directly proportional to the degree of the coccidioidal involvement A rise in the titer or its maintenance at high level indicates dissemination *Roentgenographic findings* are not conclusive The coccidioidin skin test is helpful both in establishing the diagnosis and the dose of coccidioidin to be used in the treatment The lowest dilution which gives a positive reaction is used in the treatment of this condition

velop residual cardiac lesions The cardiac involvement is the most serious and the most common feature of rheumatic fever

The significant laboratory findings are rapid sedimentation rate, leukocytosis, hypochromic anemia, and an electrocardiogram showing a prolonged P R interval *with changes in the QRS, ST*, and *T* waves There are cardiac arrhythmias and the QT which is supposed to reflect cardiac systole is prolonged In 60–80 per cent of the patients the electrocardiogram will show transitory abnormalities

Other laboratory tests used to establish a diagnosis are the antifibrinolysin test and the antistreptolysin test A diagnostic therapeutic trial with salicylates will usually confirm the diagnosis Patients with rheumatic fever respond symptomatically to the drug There is decreased pain, swelling and tenderness of the affected joints

Treatment

Active Phase There is no specific cure for rheumatic fever The objective of treatment is reduction of the load on the heart, and minimization of cardiac damage *Absolute bed rest during the active phase* of the disease is imperative This means feeding of the patient and providing bed pan service

Salicylates do not affect the proliferative phase of the disease they simply control the exudative process and pain Derivatives of salicylic acid in the form of sodium salicylate or acetylsalicylic acid are used in the treatment of acute rheumatic fever There is little difference between the two drugs in their antirheumatic effect However, some patients may be sensitive to sodium salicylate and not to acetylsalicylic acid, and vice versa

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Treatment

Before any treatment is instituted, every patient suspected of having a blastomycotic articular lesion should receive a diagnostic skin test The test is carried out as follows 0 1 cc of standard *Blastomyces* vaccine is injected intracutaneously and the area of injection is observed for twenty four to forty-eight hours The size of the erythematous reaction determines the procedure in the treatment

When the erythema at the site of injection is of less than 1 cm diameter potassium iodide may be given rapidly When the reaction is greater than 1 cm it is indicative of hypersensitivity and the patient should be desensitized by injecting subcutaneously dilutions of 1 100 1 1000 and 1 10 000 of *Blastomyces* vaccine The strength of the dilution used is determined by the reaction of the skin test The initial dose is 0 1 cc of the dilution selected, and this dose is increased by 0 1 cc every other day until 1 cc of the vaccine is given This procedure is repeated with the next lowest dilution until the undiluted vaccine is given One cubic centimeter doses of undiluted vaccine should be given concurrently with potassium iodide and continued until all symptoms subside

The administration of potassium iodide is started about ten to fourteen days after the undiluted vaccine therapy is begun It is imperative that the iodides be administered cautiously, starting with small doses

An initial dose of 0 2 cc of saturated potassium iodide in 60 cc of milk is given orally three times daily after meals This dose is increased daily by 0 062 cc until 1 2 cc three times daily, are given At this point the dose is reduced to the original 0 2 cc three times daily and the original procedure is repeated

Surgical procedures should be delayed until the patient has been desensitized Surgical interference is indicated when drainage is inadequate

Rheumatic Fever

RHEUMATIC fever is an acute exudative and proliferative inflammatory condition of the articular and cardiovascular structures, associated with Group A *Streptococcus hemolyticus* infection In the United States there are approximately 200 000 to 250 000 new cases each year and there are about 30 000 to 60 000 deaths yearly as a result of rheumatic fever

Diagnosis

It is characterized *anatomically* by fibrinoid degeneration of the connective tissue, submiliary granuloma of the mesothelial lined cavities and joints, fibroblast proliferation, and scar formation

Rheumatic fever is characterized *clinically* by an abrupt or insidious onset, usually three weeks after an attack of acute tonsillitis or pharyngitis There is fever, the pulse is rapid, and perspiration is profuse The joints are usually symmetrically involved There is pain, redness swelling, and tenderness of a migratory nature As a rule there are no articular residual effects in children While the articular manifestations are more common in adults carditis is more frequent in children About one third of patients with rheumatic fever de

* See also Chapter 10

should be feeding himself, while sitting up in bed Then the period of sitting up in bed can be increased If this is well tolerated the patient can be allowed to sit in a chair, but other activity should not be permitted If signs of reactivation are not evident after ten to fourteen days of trial he is permitted to walk on level ground *This is followed by short attempts at climbing stairs Then further exercises* are begun, if there are no signs of relapse Exercises should never be carried to the point of exhaustion or fatigue

Since active rheumatic fever is associated with the Group A hemolytic streptococcal infection, it may be advisable to use a sulfonamide to prevent a recurrence Sulfadiazine, 1 Gm daily, given orally, from October to June for four to six years has been suggested This drug should be used only after all activity of the disease has ceased

It has been shown that the administration of oral penicillin to children who have had rheumatic fever is effective in reducing the incidence of throat infections and rheumatic fever recurrences For one week of each month throughout the school year, 300 000 units of oral penicillin is given 3 times daily, one hour before meals

Rheumatoid Arthritis

RHEUMATOID ARTHRITIS is an articular and periarticular manifestation of a systemic disorder of unknown cause The disease is more common among females than males, the ratio being 4 1

Diagnosis

Rheumatoid arthritis is characterized *anatomically* by periarticular soft tissue swelling Later, there is proliferation of the synovial membrane with pannus formation, destruction of the articular cartilage, decalcification of the bones, and muscle lesions, "nodular polymyositis"

The disease is characterized clinically by a symmetrical polyarticular fusiform swelling, *with pain* and *stiffness,* most commonly of the proximal interphalangeal or the metacarpal phalangeal joints of the second and third fingers of both hands The other joints involved, in order of frequency, are the wrists, toes, elbows, knees, ankles, shoulders hips, and infrequently the spine The disease, unless successfully treated, is progressive and may lead to muscular atrophy, deformity, subluxation, and fibrous or bony ankylosis

The significant *laboratory findings* are an elevated erythrocyte sedimentation rate, a *hypochromic anemia, leukocytosis,* and a shift of the Schilling index to the left The *roentgenographic findings* in the bones and joints are characteristic There is early decreased density of the bones and periarticular soft tissue swelling Later one finds narrowing of the joint spaces, due to thinning and destruction of the cartilage, punched out bony areas due to the destruction of bone, and irregularity of the articular surfaces with evidence of dislocation and subluxation

Treatment

Since the etiology of rheumatoid arthritis is not established, the treatment of this disease is not satisfactory There is no cure for rheumatoid arthritis but progress of the disease can be arrested or reversed Since rheumatoid arthritis is a systemic disease, the patient as an individual should be treated, not simply the articular disorder Rheumatoid arthritis is a progressive *crippling* disease and therefore

nausea, and vomiting may appear within the first few days of treatment, and are simply the result of local gastric irritation from the drug These symptoms usually subside without interrupting the administration of the salicylates However, when these symptoms appear later in the course of treatment and persist for a week or longer, it probably indicates that the salicylate level of tolerance has been reached The drug therefore should be reduced or the sodium bicarbonate increased

The more severe toxic reactions from salicylate administration are mental confusion hyperpnea leading to respiratory alkalosis and finally delirium The drug should be discontinued when these toxic symptoms occur It may be advisable to administer lactate Ringer's solution and dextrose intravenously until all signs of severe toxicity have subsided

When oral administration of a salicylate is not feasible because of local gastric irritation, nausea or vomiting the drug can be administered rectally three times daily in 4 Gm doses dissolved in 120–180 cc of lukewarm starch water

The administration of salicylates for a prolonged period may reduce the prothrombin level of the blood with a resultant hypoprothrombinemia decreased coagulation time, and hemorrhage The hemorrhagic tendency may be inherent in rheumatic fever and the lowering of the prothrombin time is not serious It can be corrected by the administration of vitamin K in 5 mg doses daily

Aminopyrine may be substituted for salicylates only when salicylates cannot be tolerated This drug is as effective as the salicylates and does not produce local gastric irritation There is however the greater danger of inducing agranulocytosis A total dose of 2–3 Gm in twenty four hours for the adult and 1–2 Gm for children, in divided doses given orally every four hours is recommended The drug should be continued until the symptoms of rheumatic fever have subsided Blood counts, especially the white count, should be taken at weekly intervals during the administration of aminopyrine The drug should be discontinued when the leukocyte count is below 4000 per cu mm Penicillin 300 000 units daily should be administered without delay at the first signs of leukopenia or agranulocytosis, and continued until the blood picture has returned to normal

In cardiac failure associated with rheumatic fever, the use of diuretics and a low sodium diet are probably more beneficial than digitalis Mercuhydrin, 1 cc per 75 Kg body weight injected intramuscularly once or twice weekly and continued until there is no further evidence of cardiac edema is recommended Digitalis should be used only in the presence of frank congestive heart failure It should be used by therapeutic trial and discontinued if found ineffective As the incidence of digitalis toxicity in acute rheumatic carditis is high it must be used with caution No satisfactory guide for dosage can be recommended A well balanced, high caloric high vitamin diet also is indicated

Inactive Phase A patient is said to be in the inactive phase of rheumatic fever when the pulse during sleep is below 90 per minute and when the temperature, erythrocyte sedimentation rate, leukocyte count and the electrocardiographic findings are normal The patient is not to be allowed out of bed for one month after the rheumatic fever is judged to be inactive

The presence of a murmur is not a contraindication for resumption of activity When the patient is finally permitted out of bed the resumption of activity should be gradual and the patient should be carefully observed for relapses for six to twelve months

The first activity allowed the patient

one or two hours' duration Complete bed rest is imperative in the presence of fever or when the affected joints are painful on weight bearing The patient should be allowed out of bed gradually, as soon as the temperature is normal, or when weight bearing is no longer painful Those patients who do not require complete bed rest should rest for two hours daily Careful supervision of the affected joints while the patient is in bed should be carried out following the recommendations given under 'gonorrheal arthritis'

The *removal of infected foci* will not cure rheumatoid arthritis It is, however, to the patient's advantage to have infected foci removed, as soon as the condition permits surgical interference Teeth should be extracted only when they are proved by roentgen ray to be infected or nonvital Those foci that can not be removed should be treated medically

Salicylates alone frequently are not sufficient for the control of the joint pains A combination of acetylsalicylic acid, 0 6 Gm, phenobarbital, 30 mg and codeine, 15–30 mg three or four times daily is usually sufficient to keep the patient comfortable There is never any indication for the use of morphine in rheumatoid arthritis

Diet There is no specific or curative diet for rheumatoid arthritis The diet should be adapted to the patient's physical needs, and not the patient to the diet Patients suffering from this disease, like patients with other diseases, have a low vitamin plasma content For this reason they should have supplementary vitamin feedings However massive doses of vitamin D are useless in the treatment and may be definitely harmful especially when administered over a prolonged period

Heat and Massage Local heat in any form that is most comforting to the patient should be used Included are hot moist packs hot tub baths infrared and ultraviolet light contrast baths and whirlpool baths The physiologic effect of all heat is to increase the local circulation through vasodilatation There is an increase in local metabolism and relaxation of muscle spasm

Massage is extremely beneficial following the local application of heat It should not be carried out during the febrile period or when the affected part is acutely inflamed

Exercise Active exercises, general and of the affected parts should be started as soon as the patient will tolerate them The object of general exercises is to correct postural defects and bodily alignment The exercises should not exhaust the patient should not leave him tired and should not increase the pain of the affected parts The local exercises should be done slowly and rhythmically through the full range of motion of the joint The joint should never be forced, pulled jerked or twisted Increased pain in a joint for longer than two to three hours following exercise indicates that the exercises have been too strenuous, and should be discontinued They should be resumed after several days of rest One half hour of general rest and relaxation should follow each period of exercise *

Surgery There are several operative procedures that may be undertaken only after conservative management has failed These include synovectomy, arthrodesis and arthroplasty No surgery should be undertaken until all activity in the joint has subsided A *synovectomy* is indicated when the proliferated synovial membrane interferes with the satisfactory function of a joint, especially the knee *Arthrodesis* is indicated in a painful weight bearing joint where only a few degrees of motion is present It is useful in rheumatoid involvement of the midtarsal joints It is better to have a fixed painless joint than a painful joint with only a few degrees of motion *Arthroplasty* is the construction of a new

* For detailed exercises see end of this chapter

energetic measures should be employed to reverse the destructive changes

Chrysotherapy Chrysotherapy has been used successfully for the past twenty years in the treatment of this disease Although gold is not specific in the treatment of rheumatoid arthritis, it is the most valuable single agent used in its treatment, but, to be effective, must be used early There is a common belief that the use of this drug should be postponed until all other measures have been exhausted This is an unfortunate approach The drug should be employed before irreversible synovial and articular changes have taken place Chrysotherapy should be used as soon as the diagnosis of rheumatoid arthritis is made

The contraindications to the use of gold are renal damage, hypertension hepatic dysfunction, pregnancy, diabetes mellitus, blood dyscrasias, ulcerative colitis, and a history of allergy or exfoliative dermatitis

Different gold salt preparations contain varying amounts of metallic gold The preparations most commonly used are gold sodium thiomalate (myochrysine '), which is water soluble and contains 50 per cent of metallic gold gold sodium thiosulfate (sanocrysin) which is water soluble and contains 37 per cent of gold and gold thioglucose (' solganal B oleosum') which is water soluble but suspended in oil and contains 50 per cent gold

The recommended *dosage* is 10 mg of metallic gold injected intramuscularly at weekly intervals for five weeks Following this course, 25 mg should be injected every week, till there is objective and subjective relief of symptoms, and the erythrocyte sedimentation rate has returned to normal Subsequent doses of 25 mg should be given every two weeks for three months and every four weeks thereafter indefinitely If there is no improvement after a total dose of 1 5–2 Gm of metallic gold has been given this treatment should be stopped

There is no way of predicting the toxic reaction to the administration of gold In general, the reactions are in direct proportion to the duration of the illness, especially when the disease is of more than two years duration

When gold is given, the following precautions should be taken to reduce the severity of the reactions One should look for rashes, purpuric spots and stomatitis, and a complete blood count and urinalysis should be done every four weeks to ascertain the presence of hematologic and kidney damage

The drug should be discontinued in the event of toxic reactions These occur in 25–30 per cent of the patients treated, and may manifest themselves in the form of mild or severe dermatitis, renal damage, thrombocytopenic purpura, agranulocytosis, aplastic anemia, toxic hepatitis, enterocolitis, ulcerative stomatitis and gold bronchitis The mortality rate is 0 25–0 5 per cent

Dimercaprol (BAL) should be used when exfoliative dermatitis thrombocytopenia or granulocytosis is present BAL through its thiol group competes with the tissues for the gold It combines with the gold into a stable, nontoxic compound which is rapidly excreted It is recommended that 2 5 mg per kg body weight of BAL be given intramuscularly as a 10 per cent solution in oil every six hours for two days and thereafter every twelve hours for ten days or until there is complete recovery In addition to BAL, penicillin 300 000 units daily given intramuscularly, is recommended when agranulocytosis or thrombocytopenia is present

Other Measures Chrysotherapy should not be used to the exclusion of other measures which have proved to be of value in the treatment of rheumatoid arthritis Rest should be individualized, bearing in mind that fatigue is conducive to exacerbation of symptoms Thus, it may vary from complete bed rest to daily rest periods of

25 units given intramuscularly every six hours for three to five days, a total of 100 units per 24 hours The daily dose is gradually reduced by 20 units every other day to a level necessary to maintain adequate control of clinical manifestations

Sodium intake should be restricted to 1 Gm or less daily This will help to minimize the retention of salt and water The *oral administration of 2–3 Gm of potassium chloride daily will help prevent hypopotassemic alkalosis*

Hyperadrenalism

The beneficial effects from cortisone or ACTH administration are apparently obtained from an excess of cortical hormones Unfortunately, this generally induces a state of hyperadrenalism, which is demonstrated *clinically* by *moon facies, increase* in facial and bodily hirsutism, acne, abdominal striae, increased pigmentation, and increased fat deposition at base of neck and hips Further effects associated with cortisone or ACTH administration are amenorrhea, intolerance for carbohydrates, hypertension, sodium and water retention, hypopotassemia, and hypochloremic alkalosis There is a negative balance *for potassium, calcium,* phosphate, sulphate, nitrogen, and certain amino acids There may be an increased urinary excretion of uric acid, creatine and glucose The blood coagulation is increased, there is a tendency *to thromboembolism and healing* of wounds is retarded The administration of cortisone or ACTH interferes with the localization of infection and results in diminished pain It may mask such serious *episodes as a ruptured viscus or an inflamed* appendix Many individuals become confused, some psychotic, the severity of these reactions depending on the dose of the hormone The larger the dose the more *likely the occurrence of these complications* All of these undesirable effects disappear when the cortisone or ACTH is discontinued

The *contraindications* for cortisone or *ACTH are hypertension, diabetes mellitus* psychosis, and congestive heart failure However, these contraindications are only relative and decision whether or not to withhold the use of cortisone depends on *the urgency of the arthritic process*

Rheumatoid Spondylitis

RHEUMATOID ARTHRITIS of the spine is a chronic progressive disease of unknown etiology, affecting individuals between the ages of 15 and 35 It is more common among men the ratio of men to women is 9 1

Diagnosis

It is characterized *anatomically* by a marginal sclerosis of both sacroiliac joints, bony ankylosis of the posterior intervertebral joints and the costovertebral articulations *There is calcification of the spinal* ligaments in the later stages of the disease

It is characterized *clinically* by a gradual onset of migratory pain, and stiffness, most frequently of the thoracolumbar or sacroiliac regions Less frequently it affects the cervical and shoulder regions The pain and stiffness is most marked during the *night and on arising, it is least annoying* toward the end of the day There is characteristic rigidity of the thoracic vertebrae, fixation of the ribs flattening of the chest

joint to take the place of a fixed natural one, such as an ankylosed hip It is per formed when both hips are ankylosed and the aquisition of motion in one hip would improve the usefulness of the individual

ROLE OF HORMONES

The therapeutic application of hormones in rheumatoid arthritis is an outgrowth of an earlier observation by Hench that pregnancy and jaundice have a beneficial effect on this disease Hench inferred that the anti rheumatic substance X in jaundice and pregnancy, which is respon sible for the remissions in rheumatoid ar thritis was probably an adrenal hormone This led him and his associates to investi gate the effects of adrenocortical fractions and compound E in rheumatoid arthritis Reporting on the first series of 16 patients with rheumatoid arthritis who were given cortisone, Hench observed decreased muscle and joint stiffness decreased articular pain and increased motion of the affected joints within forty-eight hours after the first administration of the hormone Complete relief of all symptoms was noted after several days of administration of cortisone Other effects were a feeling of well being improved appetite decrease in the erythro cyte sedimentation rate and increase in hemoglobin content and erythrocyte count

In some patients however the joint swelling and effusion persisted even though all other signs and symptoms were relieved It was observed that when the administra tion of cortisone was discontinued there was generally a relapse in some patients promptly and in others more slowly

The clinical effects from pituitary adreno orticotropic hormone (ACTH) on rheu atoid arthritis were quite smilar to the sults obtained from cortisone Within a w days after the initial administration ere were decreased muscle and joint stiff s decreased articular pain and increased tion of the affected joints The erythro cyte sedimentation rate decreased more rapidly than under the admin tion of cortisone

Thousands of patients with rheuma arthritis have now been treated with co sone and there is an extensive literature the subject The pattern of response nearly all patients is consistent with t first observations of Hench and associate Cortisone will produce a prompt but tem porary remission of symptoms and signs o rheumatoid arthritis It will not correct destructive changes of cartilage and bone or ankylosis of joints Neither the hopes for a miraculous cure expressed at first, nor the fears of possible permanent harmful effects from the administration of these hormones have materialized

The dose of cortisone in the treatment of rheumatoid arthritis varies from patient to patient The objective in all cases is to obtain the maximum therapeutic response with a minimum dose of cortisone The initial dose depends on the severity of the arthritic process For maximum response it is suggested that 0 1 Gm be given intra muscularly or orally every twenty four hours for seven to fourteen days or until maximum clinical response is obtained As soon as the desired therapeutic response is achieved the dose of cortisone should be reduced gradually by 10–25 mg every other day to a level necessary to maintain ade quate control of clinical manifestations without inducing symptoms of hyperadren alism The maintenance dose should be individualized and administered three times weekly When a total dose of 3 5–5 Gm of cortisone has been given the administra tion of the hormone should be interrupted for a period of four to six weeks to mini mize possibility of side effects and adreno cortical inhibition Then the maintenance dose should be resumed and continued until the total dose of 3 5–5 grams of cor tisone has again been given

The effective dose of ACTH generally is

head During inspiration the chest is raised without raising the back and during expiration the abdominal muscles are contracted

During the period of rest in bed and immobilization of the spine the upper and lower limbs should be exercised to muscular atrophy from disuse

Heat in the form most comforting t patient should be applied to the spine t or four times daily *

* For further exercises see end of this chapte

Degenerative Joint Disease

DEGENERATIVE joint disease is a chronic articular disturbance of unknown etiology in which age and trauma are contributing factors Degenerative joint disease is a common disorder of middle age including those conditions variously described as osteoarthritis hypertrophic arthritis or senescent arthritis It has been estimated that nearly every person past 50 years of age has some form of degenerative joint changes but only 5 per cent have symptoms from these changes Except when the degenerative process affects the hip joint it is not a crippling disease

Diagnosis

The disorder is characterized *anatomically* by degenerative changes in the artic ular cartilage and the subchondral bone he changes in the cartilage may be inning erosion atrophy fibrillation and rous tissue replacement The changes in subchondral bone may be marginal iosteal proliferation with lipping and ophyte formation

is characterized *clinically* by pain stiff and limitation of motion of the ted parts The fingers knees and al spine are commonly affected in n while in men the lower spine and are more frequently involved In rative joint disease of the fingers the al phalangeal joints are involved rise to the characteristic Heberden s Vhen the knees are affected there is pain stiffness limitation of motion and crepitation on flexion and extension but there is very little effusion The outstanding symptom of hypertrophic arthritis of the cervical spine is pain in the cervical region radiating to the arms

When the dorsolumbar or lumbosacral regions are involved pain may radiate to the thighs and legs This pain may be aggravated by motion coughing sneezing and straining The symptoms of sacroiliac joint involvement are pain in the lower back limited anterior flexion of the spine and frequently pain in both thighs and legs

Degenerative joint disease of the hip may be a disabling condition The symptoms are pain in the groin and along the course of the sciatic nerve extending to the kn There is limitation of motion on abductio internal and external rotation

The significant *laboratory finding* is th roentgenologic demonstration of marginal lipping and spur formation involving the articular bony margins In the later stages there is narrowing of the joint spaces due to thinning and destruction of the articular cartilage There may be decalcification and destruction of bone adjacent to the joint The erythrocyte sedimentation rate is normal

Treatment

Treatment is palliative and should be directed toward alleviating the joint dis

and diaphragmatic respiration Kyphosis and spasm of the paravertebral muscles also may be present The normal lordotic lumbar curvature is decreased or completely flattened As the disease progresses, the en tire spine, cervical, dorsal and lumbar, becomes rigid Exacerbations and remis sions are characteristic of this disease

Laboratory findings of significance are rapid erythrocyte sedimentation rate and roentgen findings of bilateral blurring irregularity, and narrowing of the sacro iliac joints and increased marginal density In the more advanced cases complete bony ankylosis of the sacroiliac joints and calci fication of the spinal ligaments are com mon In 40 per cent of the patients the cerebral spinal fluid protein is elevated

Treatment

The recognized treatment for rheumatoid spondylitis is roentgen irradiation Follow ing this procedure there is lessened pain and stiffness and increased motion There is a decrease in the sedimentation rate, but the abnormal roentgen findings remain un altered The calcification of the spinal ligaments may even be increased

The factors necessary for the treatment are as follows 140 kilovolts with 0 5 mm of copper 1 mm of aluminum filter, 50 cm skin target distance, and 150 r (meas ured in air) to each part per treatment, a total of 600 r for the first course The ports selected are the sacroiliac (12×20 cm), lumbar spine (20×8 cm), dorsal spine (20×8 cm) and the cervical spine (12×20 cm)

The sacroiliac and the lumbar regions are treated as a unit The sacroiliac is treated in the morning and the lumbar region in the afternoon, each daily for four successive days The dorsal and the cervical regions are treated during the next four days exposing one port in the morning and the other port in the afternoon A second course may be repeated in two months using the painful sites as ports and giving 150 r per day for three successive days or a total of 450 r The second course may be repeated if pain persists

Complications The unfavorable effects from roentgen therapy may be anorexia, nausea, vomiting, and temporary leuko penia Unless severe, this is not a contra indication for the continuation of the treatment In women roentgen therapy may cause sterility and the patient should be informed of this hazard Generally, one should not give more than a total of 300 r over the pelvic region of a female patient

Additional Measures While roentgen therapy decreases pain and stiffness of the spine, other measures of proved value should be used in conjunction with it Rheumatoid spondylitis has proved par ticularly resistant to the effects of ACTH and cortisone

Rest in bed, with a non sagging, firm mattress and gradually removing the pil lows is essential This should be continued for a month or until pain muscle spasm, and tenderness of the erector spinae mus cles have subsided The spine should be kept in hyperextended position thus min imizing the strain on the spinal ligaments and obtaining optimum chest expansion The hyperextension of the spine can be achieved by gradually removing the pillows from under the head If this procedure is not successful in maintaining the spine in hyperextension and the chest in expansion a plaster jacket is indicated

Deep breathing *exercises* are extremely important in the treatment of rheumatoid spondylitis It is through this effort that the costovertebral joint can be kept from becoming fixed, thereby keeping the chest mobile and expanded Forced deep breath ing should be practiced by the patient several times daily for five minute intervals It is best carried out, with the patient lying flat on his back, hands clasped behind his

heat, massage and exercise, as outlined under "gonorrheal arthritis," is extremely beneficial. Acetylsalicylic acid, 0.6 Gm., *phenobarbital*, 30 mg., and codeine, 15–30 mg. three or four times daily is usually sufficient to keep the patient free from pain.

In addition to the treatment outlined above, different forms of degenerative joint disease may require special attention. Thus *hypertrophic arthritis of the fingers* with Heberden's nodes needs little attention, except for assurance to a frightened patient that the arthritis is not the crippling type. The pain can be relieved with local heat, *paraffin baths, or contrast baths*.

Hypertrophic arthritis of the cervical spine is best treated by applying traction to the neck with a Sayre head sling. This procedure relieves radicular pain of the shoulders and arms by widening the intervertebral foramina, thus removing pressure from the nerve roots. *Osteoarthritis of the dorsolumbar or lumbosacral spine* may require in addition to the general measures, a support such as a brace or corset for the back. *Osteoarthritis of the knee joint* may remain persistently painful despite all palliative measures. This may be due to loose cartilage and bone in the joint, which act as constant irritants. Arthrotomy is then indicated.

Hypertrophic arthritis of the hip is a disabling disease. When general measures as already outlined fail to give relief, manipulation under anaesthesia and traction may relieve the pain and deformity. If pain, flexion, and adduction persist, an arthrodesis or arthroplasty should be done. When there is unilateral hip involvement, or when arthritis of the hip occurs in the aged, arthrodesis is the operation of choice for relieving pain.

Gouty Arthritis. The treatment of an acute attack should consist of colchicine, salicylates, and sodium bicarbonate. Colchicine, 0.5 mg. in tablet form, should be given *morning and evening after meals, for an indefinite period*. Acetylsalicylic acid, 1 Gm. three times daily after meals, is helpful in alleviating joint pain and acts as an urate eliminant, in conjunction with colchicine. *Sodium bicarbonate, 4 Gm. three times* daily after meals will keep the urine alkaline. This will prevent precipitation of urate calculi and minimize the gastric irritation from the salicylates. Used together with colchicine, cortisone 0.1–0.2 Gm. or ACTH 0.1 Gm. daily quickly abort the acute exacerbation of gout.

During the chronic phase, the diet avoids meat, fish, fowl, meat soups and meat extracts and beans and is high in carbohydrate and low in fat. The obese patient should be placed on a reduction diet.*

When there is complete freedom from pain, administer colchicine 0.5 mg. once daily for three successive days of each week prophylactically. 'Benemid,' a new uricosuric agent, interferes with renal reabsorption of uric acid. It may be useful during the chronic phase but has not been fully evaluated.

* See Chapter 33.

Fibrositis

FIBROSITIS is an inflammatory condition of the fibrous tissue. It may be acute, subacute or chronic. It may occur as a primary disturbance or it may be secondary to other diseases. The cause of the primary form is unknown. The secondary form may be associated with trauma, rheumatoid arthritis, hypertrophic arthritis, gout or infectious arthritides.

Diagnosis

It is characterized *anatomically* by an inflammatory *hyperplasia of fibrous tissue*, nerves, ligaments, tendons, and fascia.

comfort and removing or correcting the contributing factors. Continued trauma to a joint increases the pain and the dysfunction. The trauma may be occupational, recreational, postural, or may be induced by excessive weight. The result of trauma is usually strain on the periarticular structures, the ligaments, tendons, and muscles, thus producing pain.

Procaine Hydrochloride. Procaine hydrochloride, when injected into the periarticular structures, is of therapeutic value in relieving pain and muscle spasm. This drug paralyzes the sensory nerve endings, thereby eliminating the irritation induced by trauma. It produces vasodilatation by blocking the local sympathetic nerves, which results in an increased blood flow and muscular relaxation. While the effect of procaine is only temporary, it serves to interrupt the vicious cycle of pain and spasm. It enables the patient to use the affected joint normally, thus preventing atrophy from disuse and the formation of fibrous adhesions. Not infrequently the benefits derived from this procedure are permanent. Procaine hydrochloride is especially useful when injected into the periarticular structures of the knees, hips and shoulders.

The best results are obtained when the procaine hydrochloride (1 per cent in aqueous solution) is injected at points of maximum tenderness. These can be detected on deep palpation or manipulation of the affected joint. These tender areas should be marked with iodine and each should be injected with 5–10 cc. The total dose for one treatment should not exceed thirty cc. It may be necessary to repeat these injections daily or less frequently, depending on the severity of the symptoms. The patient should be encouraged to use the affected joint actively after each treatment.

Reactions to the drug may be due to procaine sensitivity or to the accidental intravenous administration of the dru[g] ... cases of procaine sensitivity, desensitiz[ation] should be attempted by the use of s[...] graduated doses. Accidental intravenou[s in]jection may result in convulsions. Artifi[cial] respiration and the immediate use [of] sodium amytal (0.2 Gm. injected int[ra]muscularly, or a 10 per cent solution i[n]jected intravenously) should be institute[d]. As a precautionary measure, it is importan[t] to attempt aspiration, before injecting th[e] procaine hydrochloride, to avoid the acci[] dental intravenous administration. Less significant reactions are pallor, dizziness, sweating, nausea and occasional fainting spells. It is a good procedure for the patient to take 1 tablet of sodium amytal 0.1 Gm. orally before each treatment to minimize the possibility of procaine reaction. Local injections should not be given where surgery is indicated, where there is a local area of infection, or when the patient is known to be sensitive to procaine and desensitization is not successful.

Other Measures. Other measures of proved value should be carried out in conjunction with the local procaine injections. The cause of trauma should be removed if possible. It is useless to relieve the joint strain with procaine while allowing the cause of the strain to continue. *Rest*, whenever possible, with definite rest periods during the day, is essential. There is no truth to the idea that "keeping on the move" will prevent deformity. *Overweight* acts as a traumatizing factor, especially in degenerative arthritis of the knees and feet, by placing additional strain on the ligaments and muscles of these joints. Most patients cooperate readily in reducing their weight, when made to understand that overweight is a contributing factor to their illness. A written diet, calculated to reduce the food intake from 1200 to 1500 calories a day, will achieve the desired reduction in weight.* *Physical therapy* in the form of

* See also Chapter 33

calcification of the supra / or infraspinatus *tendons or the subdeltoid bursa in approximately* 50 per cent of the patients with painful shoulders

Treatment

Acute Phase Treatment of tendinitis and subdeltoid bursitis *with or without* calcification requires conservative management The calcification unless large, is readily absorbed by any procedure that will induce hyperemia The most effective measures are roentgen therapy and procaine injection combined with aspiration of the bursa The favorable effect of *roentgen therapy* stems from the hyperemia and vasodilatation which it induces There is increased permeability and phagocytosis leading to the absorption of the necrotic tissue and fibrin A dose of 50 r over the affected shoulder given daily for four successive days is recommended Two subsequent treatments are given at weekly intervals The technic used requires 140 kv with 0 25 mm cu filter 8 milliamperes at a distance of 25–35 cm

If pain persists after the first four roentgen treatments the areas of maximum tenderness of the periarticular structures should be injected with 5–10 cc *of procaine hydrochloride* 1 per cent solution This procedure may have to be repeated at biweekly or weekly *intervals until* permanent improvement results Movement of the shoulder should be encouraged following *the procaine infiltration* to obtain the maximum benefit from this treatment

In the presence of marked effusion, irrigation of the bursa with normal saline will alleviate the joint pain and restore normal motion of the shoulder joint The procedure is as follows

With the patient lying flat on his back, the skin of the affected shoulder is aseptically prepared Two areas are chosen, one being the point of maximum tenderness usually located lateral to the coracoid process, the second area being 6–12 mm posterior to the greater tuberosity of the humerus The skin area of both regions is anesthetized with procaine, and an 18 gauge needle 5 2–7 6 cm long is introduced into the first area, and inserted under the acromial process of the scapula The needle *is directed in a posterior* and upward course After it has been inserted for 12–18 mm, the resistance of the bursal wall is felt *Upon entering the bursa a cloudy* fluid may be aspirated into the syringe The second needle is inserted at a point *posterior to the greater tuberosity about* 10 mm below the acromioclavicular joint The needle is inserted downward until bone is encountered It is withdrawn 3 mm and then directed toward the position of the first needle Procaine, 2–3 cc of 1 per cent solution should be injected as the needles are being inserted in order to anesthetize the deep structures With both needles in the bursa 40–60 cc of normal saline solution is introduced through one needle to irrigate the bursa the solution being returned through the second needle The irrigation is continued until the solution returned is clear

The *pain* in the shoulder should be controlled with a combination of acetylsalicylic acid 0 6 Gm codeine 30 mg and phenobarbital, 30 mg every four hours The use of morphine 15 mg, is not contraindicated and should be used when the above combination is ineffective in the severely painful shoulder

Local applications of *heat*, and in some instances, cold packs are comforting to the patient *Short wave diathermy when tolerated* is helpful in relieving the pain and in aiding the absorption of calcium *deposits*

Exercises at first passive and later active, should be started as soon as the acute pain *subsides* It is very important to follow up this phase of treatment until all motion has

There is serofibrinous exudate, lymphocytic infiltration, and fibroblastic proliferation which leads to the formation of fibrous nodules

It is characterized *clinically* by a sudden or gradual onset of localized or generalized pain, morning stiffness tenderness, and limited motion of the affected parts The structures involved may be periarticular, perineural, or intramuscular Nodules of various sizes may be found There are no significant laboratory findings

Treatment

There is not any specific treatment Rest in bed during the acute and subacute stages is vital The patient should be kept in bed until all signs of activity have subsided Heat in a form that is most comforting to the patient should be applied to the affected part This includes hot fomentations hot tub baths whirlpool baths, electric pad and hot water bag

Massage following the application of heat is indicated when the acute stage has subsided Massage increases the venous and lymphatic return, blood flow and absorption are increased locally The form of massage should be individualized depending on the part involved In general the massage should be gentle with pressure and firmness over the nodules

Local injections of 5–10 cc of procaine hydrochloride 1 per cent in aqueous solution, into the center of the fibrous nodule or at the area of maximum tenderness will relieve the localized pain It may be necessary to repeat the injection at frequent intervals, depending on the response to the treatment

Analgesics in the form of acetylsalicylic acid 0 6 Gm, phenobarbital, 30 mg, and codeine, 15–30 mg, given three or four times daily are usually sufficient to keep the patient free from pain

The treatment of secondary fibrositis should be directed toward the etiologic factor which may be trauma, rheumatoid arthritis hypertrophic arthritis gout, infectious arthritides, and various other conditions

Painful Shoulder

PAIN in the shoulder is a common disorder It may be acute or chronic The pain most frequently is secondary to a lesion of the supraspinatus tendon such as calcific or noncalcific tendinitis tears of the tendon or subdeltoid bursitis and periarticular fibrositis These lesions are responsible for 90 per cent of all painful shoulders

In the presence of even microscopic tears, the anatomic changes lead to either fatty or hyaline degeneration of that tendon Fatty degeneration leads to necrosis saponification and precipitation of calcium carbonate, the end result being calcific tendinitis On the other hand, when hyaline degeneration is present, neither saponification nor calcification, but serous exudation deposition of fibrin, and fibroblastic proliferation follow and the end result is noncalcific tendinitis

Diagnosis

Diseases of the shoulder joint, especially supraspinatus tendinitis and subdeltoid bursitis are characterized *clinically* by sharp pain around the shoulder region There is limited motion, particularly of abduction internal and external rotation There is extreme tenderness, either localized over the greater tuberosity of the humerus or generalized over the joint

The *roentgen examination* will reveal

Treatment

Definitive treatment for sciatica should be directed toward removing the cause Only the palliative treatment will be discussed here

The symptomatic treatment of sciatica consists of rest in bed on a firm mattress Boards should be placed between the mattress and the spring to prevent sagging A firm pillow, placed under the knees, with the knees kept in a flexed position, is more helpful than traction Heat in any form along the course of the sciatic nerve, on the affected side, is comforting Analgesics, in the form of acetylsalicylic acid, 0 6 Gm ; phenobarbital, 30 mg , or codeine, 15–30 mg , given orally every four hours, will offer considerable relief from pain In the event the cause is not discovered and the pain persists for longer than two to three weeks perineural injections of 50–100 cc of procaine hydrochloride, 1 per cent in isotonic solution of sodium chloride is of definite benefit

For perineural injections, the patient lies face downward The sciatic nerve is located by placing the tip of the thumb on the ischial tuberosity, the tip of the middle finger on the greater trochanter and the tip of the index finger will come to rest on the sciatic nerve as it emerges from the lower border of the pyriformis muscle This should be the point of maximum tenderness The skin and subcutaneous tissue should be anesthetized with 2–3 cc of procaine solution A 20 gauge needle, 15 25 cm long, is inserted at the point of maximum tenderness and directed downward and medially at an angle of 45 degrees to the skin As the needle penetrates the nerve sheath there is a sudden sharp pain radiating down the leg The needle is withdrawn slightly and 30 cc procaine, 1 per cent in isotonic solution of sodium chloride, is slowly injected in and around the nerve sheath The needle is now projected upward 12 mm , in the direction of the pyriformis muscle and 30 cc of the procaine solution is injected at this point Relief is usually immediate Injections may have to be repeated weekly

*Exercises**

NORMAL MOVEMENT OF JOINTS

The position and the number of times these exercises are to be repeated must be *adapted to the individual* patient by the attending physician

Head

1 Bend head forward
2 Bend head backward, keeping chin in
3 Bend head toward left shoulder, then straighten
  Bend head toward right shoulder, then straighten
4 Turn face to left side, then face forward
  Turn face to right side, then face forward

Trunk

1 Bend body forward
2 Bend body backward keeping abdominal muscles retracted
3 Bend body left then straighten
  Bend body right, then straighten
4 Twist body left, then forward
  Twist body right then forward

Shoulder

1 Raise arm forward and upward
2 Raise arm sideways and upward
3 Put palm of hand on back of neck then

* These exercises are reprinted with permission of the Department of Physical Medicine, Section of Physical Therapy Research and Educational *Hospitals Chicago Illinois*

urned to normal Avoidance of motion the shoulder will lead to fibrous adhe ons and secondary muscular atrophy uitable exercises are given at the end of his chapter

Chronic Phase The results of conservative management of chronic adhesive bursitis are not very satisfactory Local injections of procaine hydrochloride, 1 per cent solution in 5–10 cc doses, into the bursa at weekly intervals until the pain has subsided and the function has returned to normal is recommended The shoulder joint should be manipulated in the direction of abduction, internal and external rotation after each procaine injection The purpose of this exercise is to increase gradually the motion of the shoulder

When manipulation under local anesthesia fails to accomplish the desired results the shoulder joint should be manipulated under sodium pentothal anesthesia One should not attempt to obtain complete correction and restoration of the joint to normal at the first manipulation Nor should one force the arm The increased pain after a forced manipulation may prevent all function of the shoulder and thus do more harm than good There is also danger that forced manipulation may result in fractures of the arm Therefore the abduction and external and internal rotation should be gentle It should be repeated after maximum improvement is obtained from the previous manipulation until normal function is restored

Procaine hydrochloride, 5 cc in 1 per cent solution, should be injected into points of maximum tenderness around the shoulder joint to alleviate pain following the manipulation Movement should be encouraged to avoid the reforming of fibrous adhesions

Analgesics, heat, diathermy, and massage, are indicated, as in the acute stage These should be continued until the shoulder function has returned to normal

The first exercises recommended should be of the pendulum type, swinging the arm backward and forward and laterally This is the type best tolerated but should be replaced as soon as possible with exercises that require greater muscular effort Suitable exercises are outlined at end of this chapter

In the presence of calcification, *roentgen therapy* should be used A total dose of 60 r should be given at semiweekly intervals for a period of six weeks 50 r at each treatment

Surgery is indicated when conservative measures have failed especially in the presence of embedded calcific tendiniti with adhesions

Sciatica

SCIATICA is not a disease it is a symptom The term is applied to pain along the posterior aspect of the hip thigh and leg that is, along the course of the sciatic nerve or its branches It may be secondary to such disorders as fibrositis, lumbosacral or sacroiliac strain, ligamentous sprains or tears and herniated disk, and less commonly to lesions of the spine the spinal cord and pelvis

Diagnosis

It is characterized *clinically* by ten ness and pain over the sciatic fora There may be associated vasomotor turbance of the affected thigh and Usually there is scoliosis of the spine the concavity toward the side of the although alternating curves of the sp not infrequently observed

Lying in Bed 1 A board should be placed under the entire mattress (1/4 inch plywood) This will prevent sagging thus preventing any tendency to deformity of the upper spine

2 A small pillow (or a rolled bath towel may be substituted) should be placed under the upper back between the shoulder blades (with no pillow under the head) for periods of a half hour at least three times a day

3 It is equally important to maintain the normal curve in the lumbar region (small of the back) (a) A small soft pillow may be used under the small of the back while lying in bed

4 Sleep lying flat on the back, using only one small pillow or no pillow under the head

Exercises

Lying on Back 1 Clasp both hands under the head (a) flatten the flexed arms firmly back on the bed (b) hold position for periods of five or ten minutes at a time

2 Place towel or small pillow under upper back (a) inhale slowly and raise arms upward and backward overhead (b) exhale and lower arms to sides

3 Place hands over lower ribs, fingers hooked under last rib, (a) inhale and at the same time spread the ribs with the fingers (b) exhale and relax

Lying on Face 1 Arms stretched at sides shoulder high (a) pull in abdomen (b) raise chest, arms and head upward off the floor from the hips

Sitting 1 Place hands at base of skull fingers touching, (a) inhale and use fingers to pull upward on back of head and thus stretch spine upward (b) exhale and relax

2 Arms folded in front of chest (a) unfold arms bringing elbows sharply back (b) return

Standing 1 Stand in the corner of a room with one hand on each wall arms shoulder level palms forward (elbows bent and abdomen in) (a) slowly let the body weight go forward and force the chest into the corner

2 Grasp overhanging bar with hands shoulder width apart Suspend body without bending elbows Remain as relaxed as possible

bring hand down under arm, touching back of hand to shoulder blade

Elbow

1 Bend arm until finger tips touch shoulder, then straighten arm

Forearm

1 Elbow bent to right angle with palm down, first turn palm up next turn palm down

Wrist

1 Bend hand forward then bend hand backward
2 Move hand toward thumb then toward little finger

Fingers and Thumb

1 Bring tips of fingers to palm of hand then straighten fingers
2 Spread fingers wide apart keeping fingers straight then bring fingers together
3 Keeping fingers straight bend hand at knuckles
4 Bend thumb to center of palm, keeping thumb close to hand then straighten thumb
5 Place thumb in front of forefinger, bring thumb straight out then bring thumb

6

Hip

1 Bend hip with knee flexed
2 Move leg backward as far as possible keeping knee straight then return to starting position
3 Move leg out to side as far as possible keeping knee straight and toes pointing straight ahead return to starting position
4 Sitting with lower leg hanging down move foot of one leg inward across other leg rotating thigh outward
5 Sitting with lower leg hanging down, keeping knees together move one foot away from other foot, rotating thigh inward

Knees

1 Bend knee as far as possible
2 Straighten leg

Ankle

1 Bend foot up
2 Bend foot down
3 Turn foot in
4 Turn foot out
5 Turn foot in and up with toes bent down

Toes

1 Bend toes down
2 Bend toes up

SPONDYLITIS INSTRUCTION

Rules

1 Measure the height every week This will enable one to know whether there is any improvement in the tendency to forward bowing of the spine and consequent shortening in height

2 Rib stretching and forced deep breathing exercises should be carried on to prevent narrowing of the chest and particularly forward bowing of the upper spine One should attempt to achieve normal expansion of the chest that is, one should be able to increase the circumference of the chest about 3-6 cm on deep inhalation

3 Forced deep breathing exercises should be done at least three times a day for periods of five minutes

4 Posture training is of utmost importance because the slightest amount of forward bending and rounding of the upper back may result in permanent fixation of the spine in that position It is essential therefore that the entire body be kept at all times in proper alignment The patient should be posture conscious and try to maintain good body mechanics throughout the day (The legs of chairs to be used by patients should be so adjusted as to permit proper alignment of the spine)

27. Androgenic and Pituitary Therapy

SIDNEY C. WERNER

Androgens

TESTOSTERONE is the hormonal secretion of the interstitial cells of the testis It is a steroid with the formula Δ^4-androstene 17(α) ol 3 one The structural formula of the propionic acid ester of this compound and of the methyl derivative are represented in Figs 9 and 10

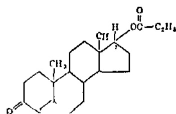


FIG 9 Testosterone (Δ^4 androstene 3 one 17 [α]-ol) Structural formula of propionic acid ester

The low rate of testosterone secretion before puberty becomes sharply accelerated at the time of sexual maturation The response is secondary to spontaneous activity of the anterior hypophysis with release of gonadotropic hormone One fraction, the interstitial cell–stimulating hormone is thought to be the activating agent

Testosterone has been isolated from the testis and has been prepared synthetically *It initiates puberty and maintains all the* secondary sexual effects attributed to normal testicular function in the adult These findings have been established in animal experimentation and in man

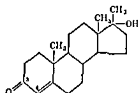


FIG 10 Testosterone (Δ^4 androstene-3 one 17 [α]-ol) Structural formula of methyl derivative

The hormone is practically insoluble in water and is readily inactivated by the liver For therapeutic purposes it is necessary to give the material in oil intramuscularly, as an aqueous suspension subcutaneously, or to employ a derivative methyl testosterone, which is not as completely inactivated by the liver, and hence is effective orally Testosterone is generally esterified with propionic acid to form testos

The Endocrine Glands

PAUL L WERMER

THE use of effective hormonal substances in the clinical practice of medicine is so recent that many of their related physiologic effects are still poorly appreciated The original concept of their physiologic activity restricted their effect to specific target organs or systems Metabolic studies of the last decade have disclosed that the action of these potent agents actually extends directly or indirectly to each component body cell A convenient concept is to consider the endocrine glands as resembling an interrelated system of weights rope and pulleys which exists in a state of equilibrium Addition or subtraction of weights causes a shift in the entire system and the establishment of a new balance Similarly when one of the endocrine glands alters its output of hormones there is a complex metabolic shift and establishment of a new endocrine equilibrium If this alteration is sufficiently profound the new state of equilibrium is recognizable clinically as an endocrine imbalance

The clinician is always faced with the problem of resolving whether the endocrine imbalance is due to primary or intrinsic glandular causes or due to some secondary factor and to direct treatment to the responsible site In his utilization of potent hormonal substances he must constantly bear in mind that with extended or high-dosage therapy complex metabolic shifts may be inaugurated which may adversely or favorably affect his patient s course To cite a few examples if one wishes to treat intelligently a woman with cardiac disease in the menopause the sodium calcium and water retaining capacity of estrogen must be appreciated Similarly the nitrogen retaining capacity of testosterone must be known for proper use of this hormone to encourage certain anabolic phenomena Insulin does more than permit the utilization of carbohydrate it affects the activity of the adrenal cortex the liver and cardiac muscle For these reasons the following chapters while primarily discussing the therapeutic action of hormones includes considerable physiologic data to orient the physician to their wide effects upon metabolism

testosterone implanted locally in the testis will prevent the cessation of spermatogenesis which follows hypophysectomy Such implants will also restore a limited degree of spermatogenesis next to the implant after atrophy from hypophysectomy has occurred

Testosterone is metabolized in the liver The degradation products are excreted largely in the urine as ethereal sulfates and glucuronides These compounds with a ketone grouping in the 17 position, the neutral 17 ketosteroids can be readily assayed after hydrolysis by the Zimmerman reaction The 17 ketosteroids of testicular origin normally constitute about one third of the total neutral 17 ketosteroid excretion the other two thirds being of adrenal origin The administration of testosterone or testosterone propionate results in an increased 17 ketosteroid excretion sufficient to account for about half the injected material Methyl testosterone is metabolized differently than testosterone A fall rather than a rise in 17 ketosteroid output may follow its administration presumably because of anterior pituitary depression by the excess hormone

THERAPEUTIC INDICATIONS

Testosterone is used as replacement or substitutive therapy When lack of testis secretion is secondary to causes other than primary gonadal failure such as malnutrition systemic disease or hypothyroidism it is a sound general principle to correct the fundamental disorder when possible rather than use testosterone Testis function will almost certainly, be re established However an empiric use of the hormone has been developed in the treatment of carcinoma of the breast

Eunuchoidism

A genetic fault maldescent of the testes with inability to emerge from the abdomen or interference with blood supply with consequent aplasia occurring before or during puberty may result in failure of or limited, sexual maturation The testes if present remain infantile Some workers believe that pituitary gonadotropin failure is the primary fault in some of this group Replacement therapy with testosterone, or the methyl derivative, is definitive and dramatic except that spermatogenesis is not induced Such therapy should be initiated only after it is certain that spontaneous puberty will not occur, generally after sixteen years of age Another indication for treatment is the demonstration of castrate levels of gonadotropin excretion in the urine

Therapy may be started and continued orally with methyltestosterone A daily dosage of 50 mg usually is required Tablets containing 10 and 25 mg are available and the total amount may be given in divided dosage Some patients may need up to 100 mg daily a few as little as 30 mg each day

Methyltestosterone in a gum tragacanth vehicle for sublingual use also is available The direct absorption of the hormone into the peripheral circulation is held to bypass the liver and avoid inactivation of the drug However there are certain objections to this route A certain amount of hormone is invariably swallowed The sublingual route is a cumbersome way to administer sizable doses of the hormone Finally, it remains to be proved that the hormone is more effective sublingually than orally milligram for milligram Evidence indicates relatively little inactivation of methyltestosterone by the liver

If the oral or sublingual routes are not available unmodified testosterone can be administered Testosterone is largely inactivated by the liver so that oral usage is precluded Testosterone propionate in oil 25 mg per cc can be given intramuscularly in doses of 1 cc three times weekly This dosage produces approximately the same effect as 50 mg of methyltestosterone daily, orally The intramuscular route is

terone propionate, in order to lessen the rate of absorption from the oily depot after injection

The clinical syndrome of eunuchoidism, i e, testicular failure with consequent inability to mature sexually has permitted detailed studies of the effect of replacement therapy with testosterone It is apparent that the so called male hormone is not limited in its effects to the secondary sex structures but is a systemic agent as well

The secondary sex characters of the male develop and are maintained functionally by testosterone secretion and may recede in its absence These include the penis, prostate, and seminal vesicles The acid phosphatase, frequently found in the blood in carcinoma of the prostate, is actively secreted by the prostate under stimulus from testosterone

The secondary sex hair of the axilla, pubic area face, etc is also included in the sphere of testosterone effect Some pubic hair growth may occur in eunuchoidism from the effect of adrenal androgens without testosterone, this accounts for the continuance of some sex hair growth after castration Head hair is not a secondary sex characteristic, but the work of Hamilton reveals that some forms of baldness may be a consequence of continued testosterone secretion

The skin also responds to testosterone It changes at the time of pubescence This is manifested first by an increase in thickness due to epithelial proliferation Next, development and increased activity of the seborrheic glands occurs The latter is responsible for the seborrhea and acne of the adolescent and adult Also pigmentation of the skin increases Finally the vascularity of the skin is increased with an increase in arterial blood flow

The voice, being a secondary sex characteristic changes at pubescence This is caused by the secretion of testosterone which increases the size of the larynx and the vocal cords The male breast generally remains quiescent but so called 'puberal mastitis probably results from the duct proliferation capacity of the male hormone to cause duct proliferation

The central nervous system responds to testosterone by an increase in libido Both sexes appear to be so affected

The systemic effects exerted by testosterone are even more striking Both muscle and bony growth are accelerated by the appearance of circulating testosterone prior to sexual maturation There is associated retention of nitrogen, as shown by Kenyon, indicative of tissue synthesis Epiphyseal maturation is accelerated along normal pathways and pathologic growth cannot be attained In the castrate, return of muscle strength follows testosterone replacement In both castrates and adolescents, creatinuria is suppressed and the basal metabolic rate is increased by testosterone about 5 to 10 per cent over former levels This probably accounts for the normal difference in metabolic rate between the sexes

Testosterone increases the erythrocyte count hemoglobin and circulating blood volume This accounts for the higher count and blood volume of the adult, and for the slightly higher blood counts of men compared to women Recent work indicates that a few obscure anemias may respond to testosterone although they are unresponsive to iron and liver

Finally testosterone is related to pituitary function and spermatogenesis The hormone is capable of suppressing the output of gonadotropin from the pituitary gland, the interstitial cell–stimulating fraction and the tubule stimulating fraction which is responsible for the initiation and continuance of spermatogenesis Spermatogenesis therefore, is sharply reduced or ceases upon administration of testosterone in large dosage On the other hand, there is ample evidence, from animal studies, that

route of administration, and duration of therapy have been fully discussed, under "Eunuchoidism" One added precaution is necessary for treatment of the adult whereas castration produces dramatic reduction of the activity of carcinoma of the prostate and its elaboration of acid phosphatase, resumption of male hormone therapy will reactivate the tumor

Male Climacterium, or Primary Postpuberal Gonadal Failure

Success has been claimed in the treatment of the male climacterium with testosterone replacement Many clinicians believe that the entity of male menopause is not a distinct one Others who believe in its existence agree that it is rare A recent questionnaire sent to twenty large clinics in this country and abroad revealed much disagreement concerning the characteristic features of the disorder and the laboratory findings by which it may be diagnosed It is safe to say that as yet proper criteria have not been constituted, if the disorder exists, to warrant the unrestricted use of testosterone therapy when the disorder is suspected but not confirmed. Also it should be remembered that the factor of suggestion is great in any use of male "sex" hormone and may be responsible for a favorable result rather than the hormone itself A fundamental psychoneurosis may be overlooked or made resistant to psychotherapy because of an unyielding conviction that the male climacterium, an organic disorder, must be present in patients with vague, although suggestive, symptomatology Involutional melancholia similarly may be neglected Finally, spermatogenesis may be suppressed, although this objection is generally not serious in this age group

Miscellaneous Disorders

Simmonds' Disease or Panhypopituitarism In patients with destruction of the anterior pituitary and associated panhypopituitarism striking nitrogen retention with re-establishment of sense of well being and of muscular strength may result from testosterone therapy Both sexes are benefited equally A dosage of 50 to 100 mg per day of methyltesterone by mouth or 25 mg of testosterone propionate intramuscularly three or four times weekly is usually adequate Other dosage forms discussed are available Methyltestosterone jaundice may be more frequent in this group

Frohlich's Syndrome or Adiposogenital Dystrophy The syndrome, by definition requires a destructive lesion in the neighborhood of the hypothalamus and the anterior hypophysis, with consequent failure of sexual maturation, and mild obesity If these criteria are fulfilled, the therapeutic indications for testosterone follow those outlined under "Simmonds' Disease" Care should be taken not to treat for this syndrome the obese but otherwise normal boy whose puberty is perhaps delayed These boys almost invariably mature spontaneously

Dwarfism or Retarded Growth Growth can be stimulated by testosterone therapy before the epiphyses have closed The limited degree of growth which is attainable and the undesirable side effects generally restrict such therapy to a small group of children in the 14 to 16 year old period in whom hereditary, nutritional or other *factors cannot be demonstrated* Usually smaller doses of 10–30 mg of methyltestosterone daily, or the equivalent of testosterone two or three times weekly are given

Maldescent of the Testis The shortening of the gubernaculum testis by means of testosterone has led to its administration to produce testicular descent However, the possible inhibitory effect on testicular development probably makes it preferable to use chorionic gonadotropin for this purpose It is important to remember that serious troubles from uncontrolled

not suitable for chronic replacement therapy in view of the quantity of oil which ultimately must be injected

Aqueous suspension of testosterone crystals 25 mg per cc, circumvents the objections to an oily menstruum Slower absorption permits weekly or semi weekly injection of 1 cc with the same effect as the oily preparation three times weekly There is still inadequate clinical experience to document this claim Long acting compounds currently are being tested Definite effects can be noted up to three weeks after a single injection

Pellets of testosterone are available for subcutaneous implantation, usually as 75 mg doses Three to six pellets are implanted beneath the skin through a special trocar or by operation A slow rate of absorption insures an effect for several months However, dosage cannot be controlled accurately, suboptimal dosage is common and occasionally local irritation or sloughing may occur

Percutaneous administration of steroid hormones has also been employed However, the dosage of testosterone required to produce a physiologic response is too large to have made this method practical

It is important to provide adequate dosage of male hormone Otherwise, physiologic response may not ensue or may be suboptimal Even with adequate dosage a lag of one to two months may be noted before erections, penile development and mild acne appear There are the first manifestations of a response Later ones include sexual hair growth muscular development body growth if the epiphyses are open and the other physiologic effects previously listed It is important to continue therapy without interruption once it is begun Cessation of progress or actual regression may occur upon discontinuance of therapy

That such regression may be especially striking in terms of muscular strength is illustrated by one of the author's patients This man a eunuchoid, had become normally adult in appearance following four years of replacement therapy Accordingly, he was accepted for military service despite his gonadal failure Methyltestosterone was not made available The patient did well till six weeks after discontinuance of the drug when he broke down during an enforced march Following discharge from the Army on this account, weakness and pain in the lower extremities continued Diagnosis of organic weakness was made and the disorder vanished upon reinstitution of methyltestosterone, after complete unresponsiveness to previously administered placebos

To attain a degree of sexual maturation comparable to that taking place during normal adolescence may require a period of several years It is still not known at what age or after how many years of testosterone therapy, it becomes advisable to discontinue the drug The hormone became available too recently to have permitted observation of the undesirable consequences, if any, of long term replacement Recent experience of the author indicates that persistent therapy may rarely establish spermatogenesis and fertility in some eunuchoid subjects

Jaundice is occasionally seen in association with methyltestosterone therapy The jaundice is distinctive both histologically and in terms of liver function and bile flow An obstructive picture in urine and stool with a negative cephalin-cholesterol flocculation reaction, only mildly elevated serum alkaline phosphatase, and normal level of cholesterol but with a reversal of the ratio between free and esterified fractions have been found in this syndrome

Eunuchism and Castration

Testosterone offers specific replacement therapy to the male castrated before or after puberty Libido, frequency of erections, ejaculations, etc are restored Dosage,

times weekly, of methyltestosterone, 60 mg orally, daily The chief indications for therapy are inoperable breast cancer in women less than five years after the menopause and for pain from bone metastases unrelieved by roentgen ray treatment

Menopause. Occasionally testosterone may be administered in the menopause to avoid the possibility of inducing harm with estrogens in patients with a personal or familial history of cancer of the breast or uterus

Anterior Pituitary and Pituitary-like Hormones

THE hormones of the anterior pituitary, and the anterior-pituitary like hormone elaborated by the placenta and other chorionic tissues, are proteins or intimately associated with proteins The isolation of many of these in relatively pure form has been accomplished in the past few years Startling effects on human tissue have recently been reported, primarily from adrenocorticotropic hormone, ACTH or corticotropin Work with other recently purified products *is still in an experimental stage* The older crude preparations can be said to be essentially inactive in man only chorionic gonadotropin has been effective

The following principles of the anterior pituitary have been purified recently and are undergoing clinical trial growth, thyrotropic or thyroid stimulating follicle stimulating, *luteinizing adrenocorticotropic* or 'ACTH, and lactogenic In addition, chorionic gonadotropin and the hormone of pregnant mare's serum are in clinical use *All the anterior pituitary hormones* are destroyed in the gastrointestinal tract and must be given parenterally

GROWTH

Actual increase in height has not been consistently achieved in man as a result of growth hormone therapy Retention of nitrogen *has not been regularly obtained* and the material is diabetogenic possibly due to contamination Differences in preparation of growth hormone may lead to widely variable results At present, it appears that no routinely useful preparation is available and that an impracticable number of pituitary glands *would be required* to sustain growth stimulation for prolonged periods with present efficiency of extraction

THYROTROPIN

Increased thyroid activity has been induced in man by means of this material *This has been accomplished in normal men* and patients with thyroid inactivity secondary to panhypopituitarism, but not with primary hypothyroidism Diagnostic *usefulness is implied, but as yet such prep*arations do not represent the pure hormone and are available only for experimental purposes

GONADOTROPIN

The follicle-stimulating, luteinizing, and interstitial cell-stimulating fractions of anterior *pituitary gonadotropin* have not been studied to any extent in man

ACTH OR CORTICOTROPIN

*It is not agreed as to whether cortico*tropin is a single hormone or is a conglomerate of from two to four different hormones Currently available preparations are still relatively crude The work of Hench, Kendall, and their collaborators has revealed the startling efficacy of this agent in relieving the symptoms and joint

libidinous drive may result from testosterone given to preadolescent subjects

Senile Pruritus and Dermatosis Scattered reports are available of benefit from replacement therapy in the elderly with senile pruritus and other senile dermatoses Systemic therapy with testosterone must be watched for the possibility of activation of prostatic carcinoma Inunction is possible as a 1 per cent ointment or cream

Impotency and Homosexuality Castration with deprivation of testosterone secretion does not result in impotency (except after many years) or premature ejaculation These conditions and homosexuality are almost invariably psychogenic and require proper psychotherapy Occasionally local factors are responsible for impotency and should not be overlooked Suggestion may be often responsible for the beneficial results occasionally seen with testosterone therapy for difficulties with potency The effect of injections then usually becomes progressively less The danger exists that the patient will explain this loss of effect on the ground that he has become accustomed to the therapy and thus needs either stronger or different medication This fixation on an organic basis to his disorder may shut off any hope of psychiatric help

Hypertrophy of the Prostate Testosterone has been abandoned as a therapeutic agent for benign prostatic hypertrophy

Gynecomastia Although gynecomastia may represent an imbalance between androgen and estrogen production testosterone therapy is completely ineffective

Vascular Disease Numerous reports have appeared recommending testosterone in the treatment of vascular disease* The list includes Buerger s disease arteriosclerosis of the peripheral vessels coronary sclerosis with angina pectoris Reynaud s disease and hypertension Most of this work is distinguished by the lack of any control studies with placebos When controlled experiments were undertaken no more beneficial effect from testosterone was seen than was obtained with placebos

Disorders of Women Testosterone may be used in selected cases for the relief of dysmenorrhea menorrhagia metrorrhagia and breast engorgement and for the suppression of lactation Adequate diagnosis including dilatation and curettage certainly is indicated before testosterone is used for functional bleeding There is also the danger of obtaining masculinizing effects if a total of 0 35–0 4 Gm of testosterone propionate or its equivalent is used in a month The effect of suggestion must be appraised

Dosages of methyltestosterone 10 mg three times a week before the onset of menstruation has been recommended for the treatment of menorrhagia For metrorrhagia a dosage of 25 mg on alternate days has been advised The monthly total should not exceed 0 15 Gm For suppression of lactation or of breast engorgement 25 to 50 mg is given every four hours or three times a day for five or six doses from the onset of lactation about the third or fourth postpartum day

Carcinoma of the Breast Under the auspices of the Committee on Research a subcommittee of the Council of Pharmacy and Chemistry of the American Medical Association a critical study is being made of the effect of testosterone on inoperable carcinoma of the breast with or without metastases The Committee s experience has confirmed the estimate of Adair and Herrman that 30 per cent of patients experience relief especially from bone pain 30 per cent remain static and 30 per cent become worse Complications of therapy may be a lethal hypercalcemia masculinization and edema and heart failure in older people Dosage of testosterone propionate is generally 50 to 100 mg intramuscularly three

* See Chapter 11

and has been found to be a glycoprotein containing about 12 per cent galactose It is standardized in international units (I U) One international unit equals 0 1 mg of a standard powder defined by a Committee of the League of Nations

The only indication for use of this hormone which has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association is in the treatment of undescended testis Such treatment is successful when mechanical obstruction does not exist Failure to produce descent usually does produce a somewhat larger gonad than existed before the treatment and so facilitates operation

A dosage range of 200 to 1000 I U two to three times a week is recommended for from six to eight weeks but not longer Signs of precocious puberty may appear and constitute a contraindication to further therapy Neutralizing substan hormones rarely have been desc appearing in the serum of patient chronically with chorionic gonadot

PREGNANT MARES SERUM HORMONE

The serum of the pregnant mare contains a gonadotropic substance with fo stimulating properties This has highly purified and a standard set Committee of the League of Nations forts have been made with this materia produce ovulation in women with anovu tion and increased spermatogenesis in m with oligospermia No clear-cut eviden of efficacy in these respects has been forth coming and therefore the claim has no been accepted by the Council on Pharmacy and Chemistry of the American Medical Association

Posterior Pituitary Hormones

THE posterior lobe of the hypophysis is under control of the central nervous system Three major effects of the crude extract are demonstrable First there is a marked oxytocic action causing uterine contraction This varies with the species stage of estrus or menstrual cycle the presence or absence of pregnancy and the stage of pregnancy Second there is a stimulating effect on other smooth muscle such as in blood vessels which causes a rise in blood pressure and causes increase in tonus in the intestine wall Third there is a marked antidiuretic action presumably from increased reabsorp ion of water by the renal tubules The rude extract of the posterior pituitary nd two purified fractions are available nically

pha hypophamine (Pitocin)

This preparation preserves the oxytocic on of the crude extract but contains less than one half unit of pressor activity per cc as assayed by the method of Hamilton and Rowe Indications for use are found in obstetrics to stimulate uterine contractions against uterine atony and against postpartum as well as postoperative hemorrhage Most authorities advise against its use in the first and second stage of labor It is also contraindicated in contracted pelvis Dosage is 0 3 to 1 cc intramuscularly If the drug is used before delivery is completed small doses are used repetitively every twenty to thirty minutes if necessary

Beta hypophamine (Pitressin)

This preparation contains the pressor and antidiuretic principles of the posterior pituitary It is standardized so that each cubic centimeter contains 20 Hamilton and Rowe pressor units twice that of the crude extract It is used in th

manifestations of rheumatoid arthritis The effects of corticotropin result from increased secretion of adrenal steroids in response to adrenal cortical activation The effects of ACTH are paralleled by those of cortisone in most respects An effect of cortisone upon the ground substance of connective tissue or upon the cellular elements involved in the early stages of fibroplasia has been shown which results in inhibition of inflammation and of connective tissue formation and repair

Therapeutic value has been found in a vast variety of diseases These favorable results almost always are not sustained when ACTH administration is discontinued The hormone must either be given continuously or its use limited to acute situations such as otherwise uncontrollable asthma or to self limited diseases such as angioneurotic edema and acute eye inflammations Some of the conditions in which ACTH has produced relief are rheumatoid arthritis rheumatic fever lupus erythematosus disseminatus allergic states, pemphigus exfoliative dermatitis inflammation of the eye and retrolental fibroplasia (Table 27) The hormone is ineffective in the absence of the adrenal glands

The hormone is contraindicated in active or recently stabilized tuberculosis where inhibition of fibroplasia may permit spread of the infection Side effects from large dosage may include exacerbation or appearance of hypertension diabetes mellitus and emotional changes with distortion of the electroencephalogram Extreme caution in use of the material is demanded, with frequent check upon the patient for these manifestations especially when these difficulties are known to exist before therapy Continued overdosage with ACTH may lead to the fullblown picture of Cushing s syndrome Peptic ulcer perforation and an increased tendency to intravascular clotting have been described during ACTH therapy Heart failure may occur Potency of

TABLE 27 CONDITIONS IN WHICH CORTICOTROPIN HAS BEEN EMPLOYED

Good response

- Rheumatoid arthritis and spondylitis
- Rheumatic fever
- Disseminated lupus erythematosus (early)
- Allergic states
  - Bronchial asthma
  - Hay fever
  - Angioneurotic edema and urticaria
  - Serum sickness
  - Drug sensitization
- Inflammatory eye diseases (including topical application)
- Exfoliative dermatitis
- Pemphigus

Variable results generally favorable

- Acute gouty arthritis
- Ulcerative colitis
- Regional enteritis
- Nephrotic syndrome
- Scleroderma (early)
- Dermatomyositis
- Psoriasis
- Periarteritis nodosa (early)
- Alcoholism
- Pulmonary granulomatosis

preparations is now standardized in units average dosage represents about 25 International or U S P units intramuscularly every six hours Twice daily injection may suffice

PROLACTIN

No clinical benefit has been demonstrated with the use of prolactin or lactogenic hormone in man This substance induces milk secretion from the crop gland of the pigeon It is believed by some to be responsible for corpus luteum secretory activity in animals and man and has been termed luteotropic hormone It has been demonstrated in the urine of women

CHORIONIC GONADOTROPIN

The urine of pregnant women contains a substance which is essentially a luteinizing hormone but which is distinct from the gonadotropins of anterior pituitary origin This substance has been highly purified

28. Ovarian Dysfunction

S CHARLES FREED

IN ANY discussion of disorders attributable to changes in ovarian function there must be a clear understanding of the physiologic activities of the various hormones whose primary action is on sexual organs or tissues Patients will differ in their symptoms and responses and the physician may be at a loss when faced with atypical manifestations unless he is acquainted with these basic actions Therefore a brief discussion of the physiologic effect of the more important ovarian hormones including use in treatment will be presented Duplication with the material presented later under specific disorders may be of benefit through repetition

Physiology

THE elaboration of gonadotropic substances by the pituitary with the consequent production of ovarian hormones results in the automatic regulation of the ovarian and menstrual cycle because of the reciprocal action of estrogen on anterior lobe secretions At the beginning of the menstrual cycle the follicle stimulating hormone is at a low level and gradually increases in amount until midcycle During this time it causes growth of the follicles with an increasing elaboration of estrogenic hormone As the secretion of estrogen reaches a peak at approximately the twelfth day it suppresses the secretion of the follicle stimulating hormone so that the follicles are no longer stimulated to grow Estrogens apparently have the ability to induce a sudden liberation of the luteinizing hormone from the anterior lobe which causes rupture of the follicle with ovulation and later a luteinization of the follicular cells

The second phase of the ovarian cycle ensues with corpus luteum formation and the secretion of both estrogen and progesterone If fertilization does not occur the corpus luteum atrophies and menstruation takes place thus ending one menstrual cycle

betes insipidus for which it exerts a specific controlling effect It is also given to raise blood pressure and to combat intestinal distention by increasing muscle tone Doses of from 0 3 to 1 0 cc are given intramuscularly, and repeated as indicated occasionally hourly for several doses For diabetes insipidus a β hypophamine tannate suspended in oil is available to delay absorption Doses of 0 3 to 1 0 cc may be given intramuscularly at intervals of thirty six to forty-eight hours

Posterior Pituitary Injection

The crude parent extract of posterior pituitary from which the preceding extracts have been derived is also used It is known as Posterior Pituitary Injection and conforms to U S P standards It generally is used only in the treatment of obstetrical problems as mentioned under α hypophamine Dosage is 0 2 to 1 0 cc, given intramuscularly or subcutaneously

Powdered Posterior Pituitary Extract

Crude powdered posterior pituitary extract may be used as a source of antidiuretic principle It may be insufflated as the powder in doses of 40 to 50 mg every four to six hours or it may be used in the form of a nasal jelly

method of assay The author has advocated the assay of estrogens by testing the response of menopausal patients under certain controlled conditions Other methods involve the use of vaginal smears and the glycogen content of vaginal mucosa In the author s opinion these latter tests are not reliable except under strictly controlled conditions since the response of these tissues to estrogen has no direct bearing on the therapeutic relief accorded patients

An important factor influencing the potency of estrogens is the rate of their absorption into the blood streams Any estrogen whose entry into the blood stream is slow will have an extended action Thus for example diethylstilbestrol is one third to one fifth as effective by injection as the more slowly absorbed diethylstilbestrol dipalmitate Estradiol dipropionate is likewise more effective than estradiol Suspension of crystals of estrogens such as estrone or diethylstilbestrol in an aqueous media results in a similar effect since the crystals remaining after *the absorption of the water* are more slowly absorbed than when the estrogens are dissolved in oil It is therefore extremely difficult to compare the various estrogens because of the large number of factors involved in standardization From a practical standpoint one can prepare a list of the estrogens in ascending order of their potency based on therapeutic responses (1) estrone and diethylstilbestrol in oil (2) estrone and diethylstilbestrol in aqueous suspension (3) estradiol benzoate (4) diethylstilbestrol dipropionate (5) estradiol dipropionate and diethylstilbestrol dipalmitate

Oral estrogens are much more readily assayed since the factor of absorption from the gastrointestinal tract is *more nearly* constant Using diethylstilbestrol 1 mg, as a standard of oral potency we believe that the following amounts of estrogens have an equal effect benzestrol, 5 mg hexestrol, 5 mg estrone, 2 mg estradiol 2 mg, estrone sulfate, 2 mg dienestrol, 0 5 mg, and ethinyl estradiol, 0 1 mg This comparison has been made on the basis of producing subjective relief in the menopausal patient under controlled conditions There is fair agreement with this opinion but due to the very nature of the test it is unlikely that greater unanimity can be obtained

TOXICITY

Common toxic manifestations of estrogens are nausea, dizziness, diarrhea, headache and edema These responses are physiologic and ample evidence exists that there is no tissue damage The toxicity of the estrogen depends chiefly on the rate of *absorption into the blood stream and may* be compared with symptoms of early pregnancy or the premenstrual phase when blood estrogen levels rise suddenly Diethylstilbestrol is toxic in this sense but this toxicity is reduced through delaying absorption by any of the means mentioned above The oral estrogens are all toxic depending upon the dosage, since their absorption at therapeutic levels is relatively rapid in practically all cases *However, it is generally* acknowledged that diethylstilbestrol is the most toxic of these estrogens the others being approximately 50 per cent less likely to produce the untoward symptoms at the same therapeutic level

Estrogens

OTHER specific actions of estrogens are (1) stimulation of the growth of the vaginal mucosa from the infantile single cuboidal cell layer to the multiple layered cornified membrane typical of the mature animal (2) growth and development of the adnexa and the uterus They stimulate the development of the endometrium and the sub mucosa, and produce a powerful myotropic action In addition they are responsible for the stimulation of mammary gland tissue, principally of the ducts

Estrogens have actions of an extragonadal nature When administered in sufficient dosage, they produce a serum calcium elevation and an increased deposition of minerals in bones Estrogens may also increase the salt and water content of the body tissue This effect is thought responsible for the edematous condition encountered in some patients during the premenstrual phase when estrogen secretion is at peak and for some of the toxemias of pregnancy Estrogens increase blood volume Their action on the vascular system is quite pronounced as is evident from the symptoms which occur in the menopause

Estrogens also have a definite action on somatic growth In the immature female estrogens in large enough amounts will cause closure of epiphyses with a suppression of skeletal growth This stunting may be due to inhibition of anterior pituitary growth hormone elaboration since administration of estrogens to growing animals causes a stunting of growth which may be orrected by the simultaneous administra ion of anterior pituitary growth hormone xtracts The typical eunuchoid female is ll with abnormally long extremities How er, there is encountered occasionally a tient with absence of ovaries who is arfed In the latter case other glands may have been involved in the stuntin growth

Estrogens not only influence the gro of the uterus but also are necessary the proper uterine response to progesteroı Apparently estrogen prepares the end metrium to become more responsive to tl action of progesterone

Metabolism

There is a definite relationship in the body between estrone, estradiol and estriol The fate of endogenous estrogens appears to involve the conversion of estradiol to estrone which in turn is transformed to estriol The liver plays a major role in this conversion reaction, as well as destroying or conjugating considerable amounts of all three estrogens Reduction in the ability to metabolize estrogen may result from deficiency of vitamin B complex or liver damage thus producing increased tissue response to circulating estrogen Therefore menstrual dysfunction may result from impairment of liver function

STANDARDIZATION

There is considerable confusion concerning the potency of the various estrogens This is in part due to the traditional use of laboratory animals for assay purposes It is now recognized that tremendous species variation exists in estrogen response Certain strains of rats and mice are sensitive to one estrogen and may be resistant to another It has therefore become necessary to depart from the use of standards based upon physiologic responses of experimental animals At the present time most estrogens are labeled by weight Within recent years the relative potency of estrogens has been based on assay in the human being using clinical response as the

adequate progesterone protection for a short time For this reason abortion is more likely to occur at this time Progesterone also acts upon the mucosa of the fallopian tubes, but the significance of this action is not too clear It also causes a proliferation of lobular cells of the mammary gland tissue following a sensitization by estrogen

Early in the study of ovarian physiology progesterone and estrogen were considered antagonists They are antagonistic in respect to cornification of the vaginal mucosa and contraction of the uterus in certain experimental animals but they are synergistic in action upon human endometrium and breast tissue

Androgens

CHAPTER 27 contains a discussion of androgens However, it may be useful to emphasize here those actions of androgens which are concerned with the therapy of ovarian dysfunctions Androgens tend to oppose the effect of estrogens on the vaginal mucosa, mammary ducts, and uterus, and may possibly inhibit certain metabolic actions of estrogens on bone and other extragonadal tissue They may also cause an atrophy of the ovaries an hormonal castration, through inhibition of the gonadotropins of the anterior pituitary

Clinical Dysfunctions

WITH the increasing knowledge of ovarian dysfunctions the complexity of factors involved in clinical disorders has been recognized The following discussion will attempt to single out the most common causes of the clinical conditions so that specific treatment can be instituted thus avoiding the commonly employed trial and error tactics

PHYSIOLOGIC AMENORRHEA

Physiologic amenorrhea occurs before puberty, during pregnancy and lactation and in the postmenopausal years A physiologic condition must be ruled out in all cases where there is an absence of menses Even the most capable physician may err in diagnosis of amenorrhea when there is a physiologic reason such as pregnancy and premature menopause There are border line cases, however, in the pubertal, adolescent years when there may be delay in maturation of the young girl, when it is indeed difficult to say whether the amenorrhea is physiologic or nonphysiologic

When menstruation does not appear by the seventeenth or eighteenth year, there is probably an endocrine disturbance either in the ovaries or other glands During pregnancy amenorrhea may lead to a faulty diagnosis when the patient is obese, rendering pelvic examination difficult or unsatisfactory In other cases of pregnancy there may be an occasional periodic bleeding to cloud the diagnosis

NONPHYSIOLOGIC AMENORRHEA

Abnormal absence of bleeding may result from a multitude of conditions many endocrine and many nonendocrine Occa

Progesterone

PROGESTERONE is the only hormone from the corpus luteum isolated in chemically pure form whose structure has been established It is known as the corpus luteum hormone Another substance has been extracted from animal corpora lutea called relaxin which has the ability to relax the ligaments of the guinea pig pelvis at term It will not be discussed here because of the questionable part played in human ovarian disorders

SOURCE

Progesterone is secreted by the luteal cells of the corpus luteum originating from the theca cells of the follicle During pregnancy the placenta takes over the elaboration of progesterone after the third month

CHEMISTRY

Progesterone is a steroid closely related chemically to other male and female sex hormones and to the adrenal cortex steroids Unlike the androgens and estrogens progesterone cannot be esterified to increase its physiologic or therapeutic activity and for this reason it is probably destroyed rapidly by the liver after administration Progesterone has recently been prepared for buccal or sublingual absorption since the liver is to a great extent bypassed by this method of administration This substance is metabolized to pregnandiol which is ex...reted in the urine coincidental with ...orpus luteum function or pregnancy Preg...andiol determination in the urine has ...en suggested as a pregnancy test because ... the increased quantities found in the ...ine during pregnancy

...thisterone (anhydrohydroxyprogester...) an oral progesterone resembles the ...on of the corpus luteum hormone on ... endometrium and vaginal mucosa of experimental animals and the human differs in certain respects, however, chie... metabolic, and there is some doubt as whether its action on the myometrium identical with that of progesterone

PHYSIOLOGY

The function of progesterone is to prepare the uterus for implantation of the ovum through the appropriate changes in the endometrium, and then to maintain this pregnant state by causing the proper environment for the embryo to develop The changes induced in the endometrium are characterized by increasing vascularity and hyperplasia of the stroma and epithelium together with growth of the secretory endometrium If the ovum is not fertilized the corpus luteum hormone is no longer secreted and menstruation occurs as the endometrial tissues lose their hormonal support and disintegrate

The action of progesterone however requires the preceding influence of estrogen on the endometrium When there is no estrogen present progesterone has little effect on the lining of the uterus Bleeding simulating menstruation can be induced in a castrate woman a day or two after the cessation of coincidental administration of estrogen and progesterone Bleeding induced by estrogen occurs after a longer period following cessation of therapy

An important feature of progesterone elaboration occurs in the human being at about the ninetieth to one hundredth day of pregnancy when the corpus luteum undergoes atrophy and its function in elaborating progesterone as well as estrogen is taken over by the placenta There may be a temporary delay in transferring this function and the pregnancy may be without

of the corpus luteum which secrete an excessive amount of progesterone, resulting in a highly developed progestational endometrium In most cases of hyperhormonal amenorrhea the uterus will be found enlarged beyond normal, especially in those cases where there are actively secreting tumors of the ovaries Removal of the cysts or tumors result in prompt uterine bleeding as the estrogen level falls past the threshold.

2 **Liver Dysfunction** Another form of hyperhormonal amenorrhea has been described relatively recently by Biskind and associates This condition exists where there is a deficiency of the vitamin B complex The liver is known to destroy or metabolize estrogens A vitamin B deficiency will reduce the ability of the liver to destroy the normal amount of estrogen which results, therefore in a relatively elevated estrogen level In such cases there is found a hyperplastic endometrium typical of excessive estrogen stimulation This type of hyperhormonal amenorrhea is probably found in some cases of malnutrition a factor known for decades as associated with amenorrhea

As a corollary any disease of the liver, such as cirrhosis and hepatitis will often result in absence of the menses possibly on the basis of a failure to metabolize estrogens

Hypohormonal *Amenorrhea*

1 **Anterior Pituitary** * Disorders of the anterior pituitary which result in an inadequate secretion of gonadotropic hormone and failure to stimulate the secretion of estrogen may result in amenorrhea *The* extreme of this condition with almost complete absence of anterior pituitary tissue is Simmonds disease

Depression of pituitary function may also result from Frohlich s syndrome Such patients are usually obese with slender extremities and heavy trunk and lack of development of accessory sex organs and secondary sex characteristics This disease is far more rare than *most physicians believe* inasmuch as numerous cases of obesity have a fat deposition resembling that of Frohlich s syndrome Neurological examination will aid in the differential diagnosis between this condition and alimentary obesity Patients with obesity due to simple overeating will mature, though occasionally late Reduction in weight will frequently hasten the process

The anterior pituitary gonadotropic hormone may also be insufficient in other cases of pituitary disorders such as gigantism or acromegaly, or other instances where a growing tumor of the anterior pituitary destroys the gonadotropic hormone secreting cells through pressure In such cases there may be periods of normal *menstrual cycles especially at the beginning* of the disease later amenorrhea ensues Cushing s syndrome which was originally thought to be solely an anterior pituitary disorder, more commonly involves disturbances of the adrenal cortex Such patients have a multitude of clinical signs *such as painful obesity, hirsutism* hypertension polycythemia osteomalacia dermatosis and so forth, so that the amenorrhea actually is of minor importance

An inadequacy of the anterior pituitary gonadotropic hormone is probably the *most common cause of amenorrhea of pi*tuitary origin The gonadotropic hormone secretion may be temporarily blocked or there may be a permanent loss of this function In cases of delayed puberty there is *said to be a temporary block* Where there is absence of gonadotropic hormone secretion the patient has an infantile sexual development

2 **Ovarian Causes** Hypohormonal amenorrhea due to ovarian dysfunction may result from a wide variety of conditions even with the ruling out of anatomic

* *See also Chapter 27*

sionally, due to language difficulties a history of a subtotal hysterectomy cannot be obtained, and the absence of bleeding may lead the physician to treat the patient with various agents Extensive curettage, radium, tuberculosis, puerperal infections, as well as other causes may be confused with nonphysiologic functional amenorrhea

Nonphysiologic functional amenorrhea has been classified as primary and secondary, primary amenorrhea being considered as a result of a disturbance of the ovaries secondary, as due to other causes The author considers this classification to be inadequate inasmuch as systemic disturbances such as malnutrition psychoses thyroid dysfunction, and so forth, may affect the anterior pituitary secretion which in turn influences the ovaries rendering the allocation of the words primary and secondary artificial It is considered more advisable to signify the type of amenorrhea by the factor which is directly responsible for the disturbance

Formerly it was considered that amenorrhea due to ovarian dysfunction was synonymous with ovarian failure It has been shown, however, with the introduction of hormone assays and the more abundant use of endometrial biopsies that amenorrhea can result from a number of different patterns in the secretion of the estrogenic hormone Frank showed that estrogen excretion of the urine in patients with amenorrhea may be either elevated above normal depressed far below normal or may be only slightly below normal This demonstration led, logically to the terming of amenorrhea as hypohormonal and hyperhormonal This apparent paradox of two opposite estrogenic states leading to a failure to menstruate has been nicely explained with clear cut clinical and experimental evidence The explanation makes use of the term 'bleeding threshold," which signifies a hypothetical titer of estrogen in the uterus (and blood stream) When the estrogen level drops below this threshold menstrual blood is released When the estrogen level is either above or below the threshold, bleeding does not take place, since it requires a fall of estrogen past the threshold to result in bleeding Amenorrhea may occur therefore, in the presence of excessive or low estrogen levels Of the two, hypohormonal amenorrhea is the more common

Hyperhormonal or Hyperestrogenic Amenorrhea

1. Ovarian Causes Hyperhormonal secretion may occur in ovaries where numerous small cysts containing active follicular cells secrete a continuous supply of estrogen This excess estrogen causes proliferation of the endometrium to the hyperplastic state The blood levels of estrogen are at a constant but elevated titer, so that there is a failure of the estrogen level to drop below the uterine threshold for bleeding It is important to bear in mind, therefore, that menstrual bleeding only occurs when the estrogen level in the blood stream, and uterus, drops past that point called the bleeding threshold A persistent elevation of estrogen, therefore will result in a functional amenorrhea

Rarely, a granulosa cell tumor may secrete sufficient estrogen to maintain the level above the bleeding threshold An enlarged uterus with hyperplastic endometrium is universally found in these cases In the prepubertal girl such tumors may induce precocious bleeding whenever the bleeding threshold is crossed

Another type of hyperhormonal amenorrhea is that associated with corpus luteum cysts of the ovary which may secrete both estrogen and progesterone in sufficient and steady amounts to prevent bleeding for indefinite periods The endometrium in these cases resembles that of the pregnancy state as shown by biopsy Certain rare tumors of the ovaries contain cells resembling those

diagnosis in an obvious case is simple except that underweight individuals are not necessarily undernourished and may receive their proper amount of food elements The diagnosis is usually made by instituting a feeding regimen The treatment will determine whether or not this type of amenorrhea is present by the response of the patient

(d) Psychic Psychic disturbances are quite common causes of amenorrhea This type may persist for months and even a year, but seldom longer The most common form of psychic amenorrhea is due to anxiety frequently over the possibility of pregnancy Resolution of the anxiety results in menstrual flow Tragedy emotional upsets or the more severe psychic disorders may induce amenorrhea for varying periods in a susceptible individual It is probable that these changes influence the ovaries through suppression of the gonadotropic hormone of the anterior pituitary via the neurohumoral pathway from the hypothalamus to the anterior lobe

Patients with anorexia nervosa because of the rejection of food over long periods closely resemble those suffering from Simmond s disease having a similar severe wasting weakness sexual infantilism, and prolonged amenorrhea Probably in these cases the anterior pituitary is suppressed as regards gonadotropin secretion but this is a functional suppression and is released upon successful psychic therapy which leads to normal food habits

(e) Adrenal Cortex Adrenal cortical tumors and hyperplasia often result in ovarian disorders principally amenorrhea These may actually be one of the first presenting signs of such disease *

HYPOMENORRHEA AND OLIGOMENORRHEA

Hypomenorrhea is a vague term signifying scanty menstrual flow It is subject to the subjective interpretation of the patient whether her periods are scanty or moderate Many women with normal ovarian function will have scanty flow and for this reason too much significance cannot be placed on the volume of the menstrual blood Nevertheless, one of the first signs of ovarian dysfunction is diminution of bleeding so that it is more important to observe the difference or change in amount of bleeding rather than the actual or absolute amount The causes of abnormal hypomenorrhea are essentially those for amenorrhea and the condition should be considered therefore as a phase in the development of amenorrhea

Oligomenorrhea is a term which signifies infrequent menstruation and has practically the same significance as hypomenorrhea Thus, it may be consistent with normal ovarian function as regards the ability to become pregnant or it may be a phase in the development of amenorrhea

DIAGNOSIS OF AMENORRHEA

As in all medical conditions the diagnosis of amenorrhea and its causes depends upon a number of procedures and methods The history of the patient should be elicited especially as regards pelvic operations or irradiation The developmental history from childhood obviously is essential in the diagnosis of primary amenorrhea The subjective complaints of the patient should be obtained for symptoms such as flushes sweats palpitation, and psychoneurotic tendencies A history of systemic diseases may also be of importance The patient should be questioned for any change in environment or psychic disturbances Food habits may point to a nutritional factor A history covering other endocrine disturbances should be obtained

The accessory sex organs are indicators of ovarian function and this is reflected in the state of the external and internal genitalia The size and condition of these

* See Chapter 30

lesions such as tumors infections, interference with the blood supply, and radiation It is only recently that adequate descriptions of the condition called ovarian agenesis have been published In such individuals there is usually a complete absence of the ovarian tissue There is failure of secondary sexual development with infantile breasts uterus and vagina However pubic and axillary hair is often found ascribed to the action of adrenal cortical steroids The patient is dwarfed the height being about four feet eight to ten inches There is lack of estrogen excretion with high gonadotropic hormone titer This condition is in striking contrast to eunuchoidism where the ovaries have either been excised or destroyed or have atrophied near the time of puberty Here the individual is tall and angular with long extremities There is absence of pubertal and axillary hair and the sex organs are atropic The laboratory hormonal findings are similar to cases of ovarian agenesis but the physical findings are distinctive The exact reason for the differences and physical characteristics of stature has not been explained as yet although other endocrine glands are probably involved in cases of ovarian agenesis The bone ages in both cases are younger than normal but much less retarded in the dwarfed patient

Ovarian masculinizing tumors (arrhenoblastoma) of rare occurrence may also result in a hypohormonal amenorrhea probably through opposition of the estrogen by androgens secreted by these tumors An xcessive excretion of ketosteroids and ndrogens in the urine is often found other tumors of the ovaries such as cysts ratomas or malignant neoplasms may so result in amenorrhea when ovarian nction is depressed

The most common type of amenorrhea to ovarian dysfunction is probably ply a subnormal amount of estrogen etion by the ovary It is at times most difficult to discover the causative factor this condition Many cases often co themselves spontaneously Those who to do so gradually develop very low es gen levels with consequent atrophy of uterus and other accessory tissues If t atrophic type of amenorrhea persists long than two years chances for spontaneo restoration of cycles becomes quite remot The longer the period of amenorrhea th less responsive is the patient to therapy

3 Extragonadal Causes There are a number of extragonadal factors which in duce a hypohormonal type of amenorrhea, which may be listed as follows

(a) Obesity It has been observed for many years that overeating with the subsequent development of overweight will gradually bring about cessation of menses, and conversely the reduction in weight will restore menses without any additional therapy Obviously many overweight individuals do not have any apparent menstrual disturbance but a number of these individuals frequently flow without ovulation and are therefore sterile It might be pointed out that practically 99 per cent of the obese cases are the simple nonendocrine alimentary type regardless of the fat distribution The percentage of true endocrine obesities has been exaggerated by the text books and the older literature

(b) Thyroid Thyroid gland disturbances may also induce amenorrhea and oddly enough both hypothyroid and hyperthyroid states may result in the absence of menses *

(c) Malnutrition Undernourishment may be another cause for amenorrhea under such conditions as exist during wars and famines Experimentally it is known that underfeeding animals results in prolonged cycles or absence of the ovarian cycle probably through suppression of the gonadotropic factors with subsequent underfunctioning of the ovaries Often the

* See Chapter 29

since the status of the pituitary, ovary and the endometrium is thus revealed Where relatively normal values are found, however in cases of amenorrhea we must place greater weight upon the history and physical findings

Pregnandiol is a substance which is considered to be a metabolite of progesterone and apparently signifies functioning corpus luteum If pregnandiol is found in the urine then it may be assumed that a corpus luteum is functioning Such determinations are no more significant than the finding of progestational endometrium

TREATMENT OF AMENORRHEA

The treatment of amenorrhea depends of course on the etiology The patient should not be subjected arbitrarily to the administration of estrogens as is so often done in treating the sign and not the disease It is of the utmost importance, therefore, to search out the possible cause If a major endocrine dyscrasia is present naturally this should be treated with all facilities available

Psychogenic amenorrhea usually responds very well to psychotherapy This may vary from simple reassurance to psychoanalysis Those cases in which a change of environment has been the causative factor will spontaneously become normal sooner or later The most common instances of delay in menses are the result of anxiety over the possibility of pregnancy This and other types of anxiety or psychic disturbances which cause a delay in menses respond to the injection of prostigmine methylsulfate The response to this drug has led some physicians to use it as a type of pregnancy test When the patient with delayed menses fails to respond to three daily injections of prostigmine methylsulfate, pregnancy must be considered Those patients who do respond are rarely pregnant Patients who do not respond may have a disturbance other than pregnancy and this constitutes a major failing of the test An animal test for pregnancy is often necessary for a differential diagnosis

Before treating other types of amenorrhea it is essential to restore the nutritional condition of the patient to normal by establishment of proper food habits If the patient shows signs of vitamin B deficiency most often demonstrated by a smooth shiny or red tongue fissures in the angle of the mouth or neuritis the supplemental use of vitamin B complex should be made This should consist of at least a daily intake of 4 mg of thiamine 4 mg of riboflavin and 60 mg of nicotinic acid together with other factors from brewer's yeast or liver Often larger amounts are required It may take several months after the establishment of proper dietary therapy before the menses return

When obesity is associated with amenorrhea proper reduction of weight often restores normal ovarian function *

In cases without major endocrine dysfunction systemic disease or developmental anomaly the physician often is confronted with a difficult task in the treatment of amenorrhea Where the state is a hypohormonal condition due to ovarian failure or abnormal development of the ovaries gonadotropic hormone therapy has often been attempted The gonadotropic hormone from the serum of pregnant mares or chorionic gonadotropic hormone are the most potent and concentrated preparations in use Chorionic gonadotropin is of extremely doubtful value since it has been conclusively shown that this material has little or no beneficial action on the human ovaries It has been used extensively in the past and has declined in popularity for the above reason

The gonadotropic hormones from pregnant mare serum and the anterior pituitary have a stimulating effect on the human ovary and upon repeated injection may be

* See Chapter 33

organs may determine the absence or degree of ovarian function although too much importance should not be placed on the size of the uterus Endometrial studies in cases in which the uterus is small often have demonstrated normal ovarian function, hence such a criterion is far more reliable than uterine size The occurrence of pregnancy in such women has also contradicted the belief that a small uterus signifies sexual infantilism The size of the breasts as well as the texture and amount of pubic and axillary hair may aid in the diagnosis of ovarian failure The length of the extremities in eunuchoidism is exceptionally out of proportion to the remainder of the body The skeletal proportion in this regard, as well as in the designation of female or male type must be made with care, as normal females may occasionally possess such measurements

In addition to routine laboratory studies of the blood and urine, there are a number of other tests of considerable importance Roentgenograms will ascertain the bone age of the individual to determine whether or not the epiphyses are prematurely closed or if closure is delayed In delayed puberty the bone age is often younger than the chronologic age This also holds true of eunuchoidism but not necessarily for ovarian agenesis where the stature is dwarfed

Endometrial studies are far more important than any other test for ovarian function, since there is less tendency for error in the histologic examination Wherever possible, endometrial strips should be obtained for examination of the degree and intensity of hormone secretion as well as the qualitative nature of the hormonal action An atrophic endometrium definitely signifies a hypohormonal condition A progestational proliferation may indicate a normal corpus luteum or a corpus luteum cyst or tumor Occasionally the endometrium may be scanty due to a past endometritis or possibly due to a refractory response of the lining of the uterus to a normal amount of ovarian hormone In such instances urinary assays for sex hormones may be of value

Vaginal smears are a fairly reliable index of ovarian function in the hands of experienced workers It is not difficult, for example, to diagnose an atrophic vaginal mucosa Nevertheless, even where there is complete ovarian failure, the mucosa may present a picture resembling that of the normal woman, possibly because of the elaboration of small amounts of estrogen by the adrenal cortex Daily vaginal smears may demonstrate in experienced hands the presence or absence of cyclic ovarian activity A persistent estrogenic smear will thus indicate ovarian activity associated with cysts of ovaries or estrogen secreting tumors

The most important assay is that of the gonadotropic hormone in the urine One or two determinations may throw considerable light on the possible cause of the amenorrhea The fundamental principle to remember is that estrogens suppress pituitary gonadotropins, and estrogen deficiency releases gonadotropins Where the gonadotropic secretion is low, we may have either absence of pituitary activity or definite ovarian activity If this is combined with a *low* estrogen value, the pituitary is probably underfunctioning Where there is a low gonadotropin with a *high* estrogen secretion both pituitary and ovarian function are present to a significant degree Where the gonadotropin secretion is above normal, i e, better than 25 rat units in a twenty four-hour collection of urine, ovarian failure is probable, and the pituitary is considered intact Assays for estrogen levels in the blood are of little value and most unreliable Thus in doubtful cases, hormonal assays combined with endometrial biopsies may throw considerable light on the cause of amenorrhea,

have responded eventually in a spontaneous manner without treatment at a later date Estrogen therapy has been described by some as like shaking the clock to make it start ticking again Where the ovaries are atrophic or unresponsive to the patient s pituitary gonadotropin, any therapy is valueless except for the control of symptoms such as flushes or sweats or for the psychic effect of uterine bleeding

In hyperhormonal amenorrhea it is of course, questionable to administer estrogens, since there is already an abundance of this material in the blood stream The cause of this state should be ascertained and if anatomic lesions such as cysts or tumors are found they should be treated in the appropriate manner In early cases of cystic ovaries the failure of the luteinizing factor of the anterior pituitary to luteinize the follicles has been suggested as the defective mechanism Gonadotropin therapy aimed to correct this condition has been suggested The results in administering any of the three available gonadotropins (anterior pituitary, chorionic, or equine) are of doubtful value, although some success has been reported Intensive therapy with estrogens has also been used on the basis that estrogens will release the luteinizing factor from the patient s own pituitary

Some authors have experienced satisfactory results in various types of amenorrhea by the use of roentgen rays to the pituitary gland or to the ovaries Such therapy should be delegated to the roentgenologist since harm may be produced by such treatment even if low dosage is used There is no satisfactory explanation for the results obtained in these cases

Ovarian resection may often re institute cycles where the ovaries have a fibrous capsule which prevents ovulation and normal cyclic activity

Dysmenorrhea

Functional dysmenorrhea is not an abnormal physiologic condition Patients with this condition have normal ovaries and grossly normal accessory sex organs The pain from the uterus may arise from nonsynchronous contractions or the woman may actually be aware of normal contractions because of a lowered threshold to pain due to a number of causes some of them emotional in nature

Relief may be obtained by preventing ovulation This may be achieved by administering 5 mg estradiol benzoate a week before ovulation is expected or by giving 0 25 mg diethylstilbestrol daily for several months In the latter instance ovulation usually occurs in spite of continued estrogen therapy Testosterone proprionate occasionally checks the pain of menstruation when administered by injection several days before menses, in doses of 25–50 mg

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding, like amenorrhea may be a sign of systemic disease endocrine disorder, or the result of ovarian dysfunction These conditions produce various patterns of ovarian function so that there may be, as in amenorrhea a hypohormonal or a hyperhormonal state Abnormal bleeding at menstruation is designated as menorrhagia and when it occurs between the menstrual flows it is termed metrorrhagia Where both are present it is referred to as menometrorrhagia

Menorrhagia

Menorrhagia occurs cyclically as in normal menstrual bleeding except that the flow is profuse and often prolonged Frequently there are clots which upon passing through the uterus produce cramps Excessive bleeding is commonly encountered in the adolescent girl although it may occur throughout the normal reproductive phase of the adult female Naturally there is a wide interpretation in diagnosing excessive bleeding some patients being more appre

able to induce ovarian activity and uterine bleeding The employment of gonadotropin in treating amenorrhea due to ovarian failure is not, however practical nor dependable in spite of the fact that these agents may be capable of stimulating ovarian function In the first place a significant percentage of cases have ovaries which are nonresponsive to gonadotropic therapy due to a number of reasons such as fibrosis of ovarian tissue or atrophy to an irreversible stage, or other anatomic changes The physician is unable to determine this without a biopsy of the ovary which is, of course not a practical procedure Secondly, those cases which do have responsive ovaries require elaborate treatment for successful results Large injections should be administered daily for seven to ten days This is expensive and inconvenient Hamblen has evolved an even more complicated treatment whereby estrogens are administered for two weeks, followed by a combination of chorionic gonadotropin and equine gonadotropin for the next ten days He claims a successful response in 30 per cent of his patients with return to normal menses following cessation of therapy Few private physicians can institute such therapy Furthermore similar results may be obtained with the simpler treatment using estrogens alone or estrogen plus progesterone, which is less expensive and more convenient

Estrogen therapy is the mainstay in the treatment of amenorrhea In the hypohormonal states a sufficient amount of estrogen therapy will induce uterine bleeding This dosage varies with the individual but on the average, 10 to 30 mg of a potent estrogen over a twenty day period will result in bleeding after an eight to fourteen day latent period of withdrawal Oral estrogens such as diethylstilbestrol hexestrol benzestrol estrone estrone sulfate estradiol dienestrol, and ethinyl estradiol are fully capable of inducing this reaction

Patients do not respond alike to th dosage Some require 500 to 1000 pe more estrogen than others in order t duce uterine bleeding If 10 mg or 2 of stilbestrol does not induce bleedin mg to 60 mg should be administered an episode of bleeding a second cours estrogen should be instituted, this o requires considerably less estrogen A t course should follow, and then the pati is permitted to go without therapy several months In about 30 per cent of t cases normal menses will follow spontaneously There is little hope for the other except to investigate further as to possibl surgical treatment for removal of cysts fibrous capsules on the ovaries, or other anatomic barriers to ovarian growth and function

Parenteral therapy will likewise perform this feat but there is no advantage over the oral medication and it has the disadvantage of being more expensive Often the induction of bleeding in such cases, even repeatedly performed will cease as soon as therapy is stopped In most patients in whom the amenorrhea is of less than two years duration, or where there is delayed puberty cycles may be re-established for a relatively long period of time Some authorities have instituted the regimen of administering estrogens followed by progesterone in an attempt to duplicate the normal cycle This has led to a rapid method for the induction of bleeding In this method, 2 5 mg of estradiol benzoate and 12 5 mg progesterone are administered together for three consecutive days Uterine bleeding will follow after a latent period of two to five days in a significant number of patients While bleeding results there is no guarantee that this is any more effective than simple estrogen therapy It has the advantage of producing more rapid results It is not improbable that those cases which respond to estrogen or estrogen progesterone therapy with a return of the cycle

Metrorrhagia

One of the most troublesome ovarian dysfunctions is that of continued bleeding from the uterus This often may be profuse and continued over a *long period of time* It has been taught for many years that such bleeding occurs from a hyperplastic endometrium More recent studies, however, have shown that metrorrhagia may occur from any type of endometrium, although there is a greater incidence of hyperplasia *Metrorrhagia is also more commonly* encountered in the older groups and has a high incidence in women who have had children The causes for this type of acyclic *bleeding are many They may be associated* first of all with certain systemic disorders or involve other glands, such as the thyroid

Malnutrition may also induce such changes and it is not unlikely that decreased vitamin B intake is the responsible factor, since this condition in turn results in a decreased destruction of estrogen with a corresponding overdeveloped endometrium Probably psychic factors also enter into this type of bleeding inasmuch as *the vascular* structure of the uterus is affected by neurogenic impulses There are a number of organic causes which are responsible including pelvic infections, tumors and other disorders These of course should be ruled out before a diagnosis of functional metrorrhagia can *be made The causes of endo*metrial hyperplasia of endocrine origin are considered due to a relative overpreponderance of estrogen This does not necessarily mean that there is an absolute increased amount circulating in the blood stream, but rather an increased ratio of estrogens over *progesterone* Thus we see that in any condition in which the estrogen secretion from the ovary is unopposed by the other ovarian hormone a hyperplastic condition may result

This may also occur in cystic *ovaries in* which the follicular cells are still active in secreting estrogen but in which there is no ovulation so that the corpus luteum does not develop The amount of estrogen in such cases may not be greater than normal In certain tumors of the ovary, such as the *granulosa cell tumor*, hyperplasia again is invariably found In such cases there may be an oversecretion of estrogen, a normal or a small amount, but the absence of corpus luteum results in hyperplasia of the endometrium due to the relative increase in estrogen In the premenopausal phase the estrogen secretion may be actually depressed with symptoms of estrogen deficiency such as hot flashes and other typical menopausal symptoms, and still there may *be hyperplasia of the endometrium because* of the absence of the corpus luteum It is even quite possible that in some cases, in *spite of the presence of the corpus luteum* hormone, the progesterone secretion may be depressed, or the lining of the uterus refractory to progesterone, so that there is again a relative overdevelopment of the endometrium to the hyperplastic state It should be noted however, that a significant *number of normally menstruating women* may have an endometrium which upon microscopic study can be diagnosed as hyperplastic It is therefore wise to avoid placing too much stress on the endometrial biopsy without considering the other features of the case Furthermore, it is well to *obtain several strips of endometrium* for study, inasmuch as in many cases there is a patchy distribution of *the hyperplasia* Actually several authors have shown that the bleeding may occur from localized areas of necrosis in the endometrium which *is* otherwise hyperplastic although others have indicated that the local necrosis is the result of bleeding and thrombus formation

We must not neglect an old theory that the endometrium is not responsible for the bleeding but that there is a separate bleed*ing factor in the pituitary* which is responsible, or other speculations that bleeding is a result of myometrial defects, principally

hensive than others in this regard In many women a heavy flow may alternate with a more moderate one The cause of menor rhagia is often obscure, although one must not overlook organic disorders such as the bleeding dyscrasias in which the clotting mechanism is at fault Certain transitory systemic disorders may alter a normal menses so that it may become heavy for a month or two Endometrial biopsies taken before the onset of flow indicate that ovulation has taken place in most cases and the endometrium often cannot be dis tinguished from normal progestational proliferation Certain glandular disorders also may be associated at least temporarily with heavy cyclic flow

Hypothyroidism often results in excessive menstrual flow although the exact reason why this state is found in association with menorrhagia is not clear especially in view of the fact that amenorrhea may also result from thyroid deficiency

Psychic factors may often result in exces sive menstrual bleeding just as amenorrhea may be the result of a psychic disturbance

Where constitutional causes are ruled out as well as local organic pelvic diseases such as fibroids endometriosis and sub involution of the uterus, the etiologic factor for menorrhagia is often difficult to find It has been suggested that there is an irregular ripening of the endometrium to account for excessive bleeding that pro gestational proliferation which signifies a response to the corpus luteum hormone occurs only in patches Pregnandiol deter minations are of little aid in such a diag nosis The fact that curettage alone often corrects the abnormal bleeding does suggest at times that the endometrium is refractory to the action of progesterone It has been suggested by some that the myometrium is at fault, and that the smooth musculature of the uterus is unable to contract about the spiral arteries sufficiently so that the openings of the spiral arteries remain wide with a subsequent profuse flow

Polymenorrhea

Polymenorrhea refers to the occurrence of menstruation at intervals of twenty days or less duration It is claimed by some that this is the result of an early regression of the corpus luteum so that its life is de creased from fourteen days to about seven days While this may be true of some women, especially around the fortieth year, nevertheless the condition also occurs in younger women It may occur also in vari ous types of disturbances such as under nutrition, psychic disorders, and infectious diseases Treatment is not urgent, since usually there is not excessive flow of blood

Intermenstrual Bleeding

Intermenstrual bleeding often occurs exactly at the time of ovulation, and may be associated with *mittelschmerz* Some times it is so scanty as to be present as spotting At other times it may resemble a menstrual flow There are two possible mechanisms for these occurrences In the first place ovulation may result in the rupture of some perifollicular capillaries so that a small amount of blood leaks down the fallopian tubes Some observers believe, on the other hand, that it is a result of engorgement of the uteru with an oozing of blood through the endometrium These two factors may be responsible for the scanty bleeding To account for the more profuse bleeding at the menstrual period a different mechanism must be postulated

It must be remembered that there is a biphasic estrogen secretion of the ovary with two peaks, one occurring at ovulation time and the other before menses Inas much as bleeding will ensue when the estrogen level of the blood drops below the bleeding threshold, it is not unlikely that the dip of the estrogen level following the peak at ovulation goes past the bleeding threshold, so that bleeding from the endometrium will resemble that of the menstrual flow

Metrorrhagia

One of the most troublesome ovarian dysfunctions is that of continued bleeding from the uterus This often may be profuse and continued over a long period of time It has been taught for many years that such bleeding occurs from a hyperplastic endometrium More recent studies, however have shown that metrorrhagia may occur from any type of endometrium although there is a greater incidence of hyperplasia Metrorrhagia is also more commonly encountered in the older groups and has a high incidence in women who have had children The causes for this type of acyclic bleeding are many They may be associated first of all with certain systemic disorders or involve other glands such as the thyroid

Malnutrition may also induce such changes and it is not unlikely that decreased vitamin B intake is the responsible factor since this condition in turn results in a decreased destruction of estrogen with a corresponding overdeveloped endometrium Probably psychic factors also enter into this type of bleeding inasmuch as the vascular structure of the uterus is affected by neurogenic impulses There are a number of organic causes which are responsible including pelvic infections tumors and other disorders These of course should be ruled out before a diagnosis of functional metrorrhagia can be made The causes of endometrial hyperplasia of endocrine origin are considered due to a relative overpreponderance of estrogen This does not necessarily mean that there is an absolute increased amount circulating in the blood stream but ather an increased ratio of estrogens over rogesterone Thus we see that in any contion in which the estrogen secretion from e ovary is unopposed by the other ovarian rmone a hyperplastic condition may ult

his may also occur in cystic ovaries in h the follicular cells are still active in ting estrogen but in which there is no ovulation so that the corpus lut not develop The amount of est such cases may not be greater than In certain tumors of the ovary, suc granulosa cell tumor, hyperplasia invariably found In such cases the be an oversecretion of estrogen, a n or a small amount, but the absen corpus luteum results in hyperplasia o endometrium due to the relative inc in estrogen In the premenopausal p the estrogen secretion may be actually pressed with symptoms of estrogen d ciency such as hot flashes and other typi menopausal symptoms and still there m be hyperplasia of the endometrium becau of the absence of the corpus luteum It i even quite possible that in some cases in spite of the presence of the corpus luteum hormone the progesterone secretion may be depressed or the lining of the uterus refractory to progesterone, so that there is again a relative overdevelopment of the endometrium to the hyperplastic state It should be noted however that a significant number of normally menstruating women may have an endometrium which upon microscopic study can be diagnosed as hyperplastic It is therefore wise to avoid placing too much stress on the endometrial biopsy without considering the other features of the case Furthermore it is well to obtain several strips of endometrium fo study, inasmuch as in many cases there is a patchy distribution of the hyperplasia Actually several authors have shown that the bleeding may occur from localized areas of necrosis in the endometrium which is otherwise hyperplastic although others have indicated that the local necrosis is the result of bleeding and thrombus formation

We must not neglect an old theory that the endometrium is not responsible for the bleeding but that there is a separate bleeding factor in the pituitary which is responsible, or other speculations that bleeding is a result of myometrial defects principall

in the spiral arteries penetrating the muscle Thus the muscle of the uterine wall normally contracts upon the spiral arteries and if this contraction is not sufficient the arteries remain open and this results in continuous bleeding

In making a diagnosis of irregular bleeding one should of course rule out organic lesions in the pelvis Endometrial biopsy is naturally essential for the diagnosis Vaginal smears may also be useful where it can be shown that there is continuous production of cornified cells and an absence of cyclic changes in the vaginal mucosa Often a slight to moderate enlargement of the uterus is coincident to hyperplasia but this is not necessarily a constant finding

Treatment In the younger groups there may be a spontaneous correction in about 50 per cent of the cases Often however the physician cannot wait for such a correction but must treat the patient immediately especially when there is extensive hemorrhage In the premenopausal group if the bleeding is not harmful there is a gradual diminution in amount and natural menopause ensues However even in these cases the bleeding may be quite extensive and therapy is immediately indicated For the control of hemorrhage we have a number of agents which are effective Such agents of nonspecific nature as calcium ergot posterior pituitary and snake venom may serve a purpose in the immediate steps to control bleeding Naturally it is of importance to correct any nutritional systemic or glandular disorder which may exist Thyroid medication is dramatic in those cases in which a thyroid deficiency exists Likewise vitamin B complex is also effective when this material is lacking in the body When the bleeding has been prolonged over a long period proper anti anemia therapy should be instituted such as blood transfusions or iron Bed rest may be essential in some cases in which the bleeding is extensive and prolonged

Endocrine therapy has proved of great value in cases of metrorrhagia Chorionic gonadotropin is not in vogue at the present There is considerable doubt as to the efficacy of this substance although there may be an occasional case which responds to its administration Other gonadotropins have been tried with varying success Equine gonadotropin in doses of 100 to 1000 international units weekly has been administered to induce ovulation and corpus luteum formation This therapy is expensive and not very certain and should be attempted only in the hands of a specialist The administration of progesterone which theoretically should be proper is on the whole disappointing The dosages required are rather large and results are not too encouraging With the availability of oral progesterone however it may be shown that such therapy is more practical because higher dosages over a longer period of time may be administered more conveniently

In practically all cases the administration of sufficient amounts of estrogen will cause a cessation of bleeding In the younger patient the dose of estrogens may be quite high 5 to 10 mg per day It is advised that *oral estrogens be used in all cases so that* larger amounts may be administered daily Stilbestrol hexestrol benzestrol and natural oral estrogens premarin estrone or estradiol dienestrol and ethinyl estradiol may be used These two latter compounds may be used in somewhat smaller dosages since they are more effective by mouth than the other oral estrogens After determining the correct dosage by the response of the patient it should be maintained for thirty to fifty days After cessation of therapy the patient may bleed again within ten to fifteen days but usually this is of normal *amount and in a considerable* number of cases regular cyclic bleeding then ensues

The explanation for this phenomenon in which a hyperestrogenism is treated by administering large amounts of estrogen may be quite puzzling It has been recognized, however, that large amounts of estrogen depress ovarian activity by depressing the output of the follicle stimulating hormone and by producing release of the luteinizing hormone of the anterior pituitary gland, so that after cessation of administration of estrogen, the normal cycle is instituted, whereby the follicular stimulating and the luteinizing hormones are released in their normal cyclic manner

In the older age groups near the menopause, rather small amounts of estrogen are effective A daily dose of 0 5–1 mg of oral estrogens, or 2 to 5 mg of injectable estrogen per week may be sufficient to raise the estrogen level above the bleeding threshold of the uterus Here again it seems a paradox to administer estrogens to individuals whose endometrium would indicate an excess of this substance If one realizes, however, that the hyperplasia may be due, not to an absolute amount of estrogen, but to a *relative one which is unopposed* by the corpus luteum hormones, the reason becomes clear The important feature is to raise the estrogen level above the bleeding threshold

In recent years there has been considerable use of male sex hormones in the treatment of uterine bleeding Practically any functional bleeding of the uterus may be checked by administering a sufficient amount of androgen The mechanism of androgen action is twofold In the first place, it antagonizes estrogen secretion by the ovary so that the estrogen level drops *and stays below the bleeding threshold* Secondly, it suppresses the anterior pituitary gonadotropic hormone so that ovarian depression results, and varying degrees of a hormonal menopause are induced The administration of 0 1 to 0 6 Gm of testosterone propionate over a period of a month will produce typical menopausal symptoms in some individuals There may also be an induction of virilism with hirsutism, acne, and a bass voice Often, however bleeding may be checked by *0 2 to 0 4 Gm* per month or less The suppression of bleeding and the menstrual cycles by such treatment may persist for two to six months following cessation of therapy Normal menstrual cycles may then return after this period of induced amenorrhea There should be caution in administering large amounts of androgens since virilism may result Some of these changes are temporary in nature and disappear in from one to four months following cessation of therapy Voice changes may persist

Other means of suppressing bleeding are well known roentgen rays or radium to the ovaries *may* be the treatment of choice when the individual is approaching the menopause, and when therapy of the endocrine type is impractical Surgery, be*cause of excessive bleeding is rarely* necessary in view of the effectiveness of the endocrine products There is little need nowadays to remove the uterus because of excessive bleeding due to a functional condition

According to Karnaky, any uterine bleeding can be checked within a matter of minutes by injecting 10–30 mg of diethyl stilbestrol directly into the cervix

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one other condition of surgical nature which results in the changes typical of the climacteric, but which has received relatively scant attention of physicians The removal of the uterus alone without interfering with the ovaries may result in a decline in ovarian function This occurs in about 40 per cent of the women undergoing such an operation As a rule, this occurs following total hysterectomy with a delay of from six to eighteen months before the symptoms arise

ORGANIC CHANGES

The typical climacteric changes may be separated roughly into two categories the functional disturbances which include the psychic and circulatory disturbances and the organic changes

The organic changes are widespread over the entire body, but the most affected organs are those which respond to the greatest degree to the stimulus of the ovarian hormones Because of the reciprocal relationship of the ovaries to other endocrine glands we note changes in these which reflect in altered function of the body With the failure of the ovarian secretion the anterior hypophysis is altered in function In the anterior lobe the gonadotropic secreting cells become hyperactive and the gonadotropic hormone content of the body fluids usually increases Some authorities believe that the increase in gonadotropin follows closely the symptomatology of the climacteric, while others find no correlation between the two since symptoms may appear in cases where no excess of gonadotropic hormone exists and conversely, few or no symptoms may exist when there is an excess of this substance Furthermore relief of the symptoms by estrogenic therapy has been observed without alteration in the level of gonadotropin

Thyroid There has been considerable speculation as to whether the thyroid gland is altered in function during the climacteric It has been demonstrated that there is an increase of certain substances in the urine which possess the ability to stimulate the thyroid gland Most of the data on the thyroid gland appear to be of a clinical nature, due to the similarity of symptoms between thyrotoxicosis and the climacteric, in both of which the patient is tense, nervous, and unstable with tachycardia tremors, and other vasomotor responses In both groups of patients the symptoms suggest an unstable sympathetic nervous system Nevertheless, too much weight should not be placed upon the similarity of symptoms and signs Fortunately a simple therapeutic test is often of value in distinguishing between the two conditions namely by administering therapeutic doses of estrogen with dramatic relief of the typical menopausal symptoms thyrotoxicosis may be ruled out

Adrenal The adrenal gland in the climacteric does not undergo any marked changes There may be, however, a functional disturbance of the adrenal cortex due to the imbalance between the estrogen of the ovary and the androgen of the adrenal cortex It is possible that there is a relative overpreponderance of androgens due to the diminished amount of the antagonizing hormone the ovarian estrogen Such a situation may account for the commonly observed increase in hair growth seen in menopausal women and also the other more or less significant decline in the feminine characteristics of the woman

Pancreas There is no concrete evidence that the pancreas is involved in any organic changes It is more likely that the increased psychic tensions of the individual are responsible for the higher incidence of diabetes It is not unlikely that some individuals may be latent diabetics and upon the change in psychic and neurovascular status of the climacteric this latent diabetes flares up The administration of estrogens which in such cases will alleviate distress

The Climacteric

THE climacteric may follow the meno pause by a varying number of months or may precede the actual cessation of menses by a few months so that these periods may be described as premenopausal, menopausal, and postmenopausal

The objective features of the climacteric may vary considerably, and are chiefly those of alterations in uterine bleeding There are a number of patterns in which uterine bleeding may change The simplest is that in which a woman will have a men strual period, after which none again appears There also is the common occur rence of gradually diminishing menstrual flows although the regularity of the cycle is not greatly disturbed A third pattern is that in which the menstrual flow becomes spaced further apart, with periods of amenorrhea lasting three to six or more months A fourth type is that in which frequent menstrual flows occur, such as one every two weeks, and a fifth type is that in which the menstrual flow may become ex cessive in amount for a number of periods preceding the actual termination of the menstrual cycle In this latter case, bleed ing between the periods is commonly en countered, so that we may have the condition of menometrorrhagia All these different patterns in which the menses may terminate signify ovarian failure with vary ing degrees of rapidity It would be most confusing to attempt to explain the various patterns of menstrual flow without a sound insight into the fundamental physiology of the ovary

The ovarian failure naturally involves a decreased amount of estrogen secretion by the ovary When the estrogen secretion de clines abruptly, the menstrual cycle likewise terminates rather promptly An occasional flare up in activity of the ovary may result in an occasional menstrual period When the ovarian activity declines more gradu ally, different patterns of abnormal men strual flow result depending upon the level of estrogen which is maintained by the ovary For example, if the level of estrogen hovers about the bleeding threshold there is excessive bleeding response with either menorrhagia or the menometrorrhagia

This difference in rate of decline of ova rian function likewise explains the peculi arities in the appearance of the symptoms of the climacteric The sudden termination of ovarian function may result in the more or less rapid onset of symptoms The more gradual decline will delay the appearance of the typical symptoms although this may also induce unusual patterns Thus a grad ual decline in ovarian function may be compatible with a continuation of regular menstrual cycles if the estrogen secretion of the ovaries is still sufficient to rise above the level of the bleeding threshold in a rhythmic manner Still the lower level of estrogen during most of the month may be such as to result in the subjective symptoms of the climacteric, thereby presenting a so called premenopausal climacteric syn drome with symptoms in a regularly men struating woman

Artificial menopause may be induced either by the removal of the ovaries by sur gery, or their obliteration by radiation by either roentgen ray or radium The symp-toms are often prompt and severe Other conditions which may result in symptoms of the climacteric due to abnormal involve ment of the ovary are multiple ovarian cysts which obliterate the estrogen secret ing cells, infections such as tuberculosis or gonorrhea, or surgical manipulations which interfere with the pelvic blood supply, leading to atrophy of the ovaries There is

low grade arthritis may be present for years, but with the development of the menopause and a lowered threshold to stimuli, pain and disability due to the arthritis become more intense Similarly, there may be a predisposition to overweight, and with the altered endocrine and psychic changes this tendency flares up In the treatment of these conditions therefore as in the treatment of all conditions which are accentuated during the menopause, the relief of menopausal symptoms by the restoration of the endocrine balance will often relieve the patient of her nonspecific symptoms The estrogens which are used for this purpose are not necessarily cures for such disturbances as arthritis obesity, diabetes and so forth, but simply bring the psychosomatic relationship to its proper or more normal position

Cardiovascular Changes The cardiovascular system is extremely sensitive to the deprivation of estrogens at the menopause in a significant percentage of women At this time a hypertension is prone to develop and with hypertension come other cardiovascular complications such as enlarged heart coronary changes and kidney damage In addition to the gross changes in the blood vessels there are disturbances in the smaller ones especially in the capillaries These vessels become more fragile so that they are very easily ruptured and grow extremely labile so as to contract and dilate upon minor degrees of excitation This is reflected in the typical hot and cold flashes and night sweats The instability of the circulatory system has also been demonstrated in changes in the electrocardiogram indicating an increased irritability of the myocardium These changes may be reversed upon substitution therapy

PSYCHIC CHANGES

The psychic changes in the menopause are well known The patients become nervous irritable emotionally unstable with either depression or excitation and tensions of all types may arise It is probably less confusing if we attempt to view the various bizarre and psychic disturbances in the following manner With the failure of the ovary to elaborate estrogens the underlying psychic pattern of the individual unconscious in many cases, is brought nearer the surface The inhibitions and control of these psychic forces are lessened so that whatever tendencies the patients have are brought into the open The outlet for the nerve tension of the individual may give rise to various disorders involving the organs which respond to psychic stimuli such as the gastrointestinal tract cardiovascular system muscular apparatus and metabolic systems

Involutional Melancholia The extreme degree of psychic disturbance occurring at this time is so called involutional melancholia Years ago many patients were classified in this group and considered psychopathic With the availability of estrogen therapy, fewer patients have been shown to fit into this category, and many either on the borderline or whose symptoms resemble those of the involutional patients have been restored to normal In the present development of the field of psychosomatic medicine, when so many functional disturbances are being ascribed to the nerve tensions of the individual it is well to be aware of the influence of the climacteric upon the status of these functional disturbances since whatever psychic drives existed before the menopause will have that much greater effect upon the body and mind subsequent to the lowering of the threshold to stimuli following estrogen deficiency In the treatment of these psychosomatic disorders probably one of the first steps is the restoration of the previous threshold level by adequate estrogen substitution therapy

TREATMENT

The treatment of the menopause has brought about tremendous benefits to large numbers of suffering women through the

will also cause considerable relief of the diabetic condition

Ovary The ovary undergoes marked alteration during the menopause The follicular structure undergoes a varying degree of atresia Cysts may form and the granulosa and theca cells are gradually absorbed With this gradual decrease in follicular activity estrogen is no longer secreted in normal amounts and this is reflected in the alteration of the secondary sex organs as well as in the entire body The ovary finally becomes atrophic and consists chiefly of fibrous connective tissue the capsule of the ovary also becomes thickened and fibrotic Occasionally ovulation may take place during the general regression of ovarian activity thus accounting for conception during menopause but as a rule the menstrual bleeding which occurs is of the anovulatory type

Breasts The most marked changes apparent to the physician are those which involve the regression in the accessory sex organs namely the breasts the uterus and the vagina The *breasts* undergo glandular atrophy with considerable absorption of the subcutaneous fat This atrophy can be reversed by the administration of estrogens so that the breasts may become engorged and actually painful

Uterus The uterus also undergoes atrophy and even fibroids and myomas may also regress since these structures are also under the influence of the estrogenic hormones The endometrium of the uterus becomes atrophic and flattened This is not universal however and some women may show a fairly well developed endometrium and in some cases a certain degree of hyperplasia This is undoubtedly due to estrogen secretion from the adrenal cortex which occurs even in the menopausal woman The hyperplasia is due to the constant estrogen secretion unopposed by any corpus luteum activity

Vagina Similar changes take place in the vaginal mucosa. In most cases there is a marked atrophy of the lining of the vagina readily seen by microscopic examination of smears The cornified cells disappear and those remaining are much like the infant's vaginal mucosa Nevertheless in a considerable number of cases a fairly well developed mucosa is seen, and even some which are undistinguishable from normal For this reason the use of vaginal smears may be unreliable either as a diagnostic procedure or for assaying estrogen therapy There is little correlation between the severity of symptoms and the degrees of atrophy of the uterus or vagina and there is relatively little correlation between the therapeutic response from estrogen therapy and the organic responses of these organs The organic changes in the vagina may occur to an extreme degree so that the condition of senile vaginitis ensues The mucosa becomes dry and friable causing considerable irritation and even localized bleeding A nonspecific discharge may be present Another condition is that which occurs with the atrophy of the vulvar epithelium since this tissue is also under the influence of the ovaries These changes are minor but in some patients may be reflected in the development of certain dermatologic changes such as kraurosis dermatitis or pruritus

Arthritis and Obesity Other organs may undergo changes coincidental with the cessation of menses in the climacteric It is of course difficult to determine whether there is a direct relationship between the ovarian failure and these organ changes or whether it is a coincidental change due to the aging of the individual Thus it has been stated that arthritis may be of menopausal origin Obesity at this time is also ascribed to the endocrine imbalance Probably a more sound view is that the menopause predisposes to the development of these conditions primarily through intensifying certain underlying tendencies Thus

standing of the various products and their potencies It is true that there has been much confusion in the past as to the relative effectiveness of the various preparations especially the estrogens the differences between the oral and the parenteral products and the best method in which to administer these agents This confusion is of course natural because of the rapidity with which the estrogens have been made available to the physician and to the difficulty in determining their relative physiologic potency Much confusion has been furnished by the competing drug firms who are anxious to impress the physician with the relative superiority of their products Favorable evidences are quoted while adverse or uncomplimentary features are suppressed

Estrogens are of course the fundamental *endocrine agents for the relief of the menopause* There are a number of ways in which a menopausal patient may receive estrogenic therapy depending upon the *severity of symptoms the cooperation of the patient and the temperament of the* physician A common method is to start the patient with relatively frequent injections of either estrone or urinary extracts containing estrone in dosages of about 1 mg *or 10 000 international units two or more* times a week depending upon the response of the patient This dosage is then continued at less frequent intervals to maintain the relief of symptoms Injections once a week *may then be supplemented* by oral estrogens such as diethylstilbestrol 'premarin benzestrol or estrone in 0 5 to 1 mg or ethinyl estradiol in 0 05 mg dosages daily as required to produce relief of *symptoms* Eventually the patient may be controlled simply by oral medication

Another method is simply to start with oral products immediately *It is advisable* in such instances to start with relatively small dosages since toxic reactions will be obtained in a significant number of individuals when therapeutic dosages are administered immediately For example daily doses of 0 25 mg of diethylstilbestrol are advised for about five to seven days and the dosage doubled at weekly intervals until therapeutic response *is obtained After this* order is established the dosage may be reduced to a level which will maintain the individual free from symptoms

A third way is to administer some of the *esters of estradiol in moderate doses at* regular intervals One half to 1 mg of estradiol benzoate or dipropionate are given in weekly dosages for a variable number of weeks, and the intervals between injec*tions gradually increased to the mainte*nance level after relief is established Still another way of treating menopausal syndrome is to commence with relatively large doses of some of the more slowly absorbed *estrogens such as estradiol dipropionate or* diethylstilbestrol dipropionate Administration of 2 5 mg to 5 mg of either of these two preparations will produce relief in *practically all cases even the most resistant The relief period after one of these injec*tions will vary from two to eight weeks even longer in some cases There is relatively little toxicity encountered after such injections although occasionally there may *be some nervousness and tension for two* or three days after such large doses It is well for the physician to remember that there is a wide range of responsiveness of patients to estrogenic therapy some patients responding to as little as 0 25 mg others requiring 5 0 mg of an oral estrogen daily Similarly the dosage of injected estrogens will also vary from 0 5 mg to 5 0 mg every two weeks

The toxic effects of estrogenic therapy are not due to any organic damage to tissues or organs Toxicity is manifested by symptoms such as nervousness irritability headache dizziness nausea and vomiting and diarrhea These symptoms are probably

advent of the modern estrogen therapy Nevertheless, the administration of estrogen alone does not always make for complete relief of symptoms in a significant number of patients It is indeed difficult to separate clearly the various factors in the treatment of these patients The three main agents used in treatment are general medical therapy, psychotherapy, and hormonotherapy These three methods are intertwined and inseparable, since the administration of any agent regardless of its specificity or physiologic effect will often benefit the patient simply through the power of suggestion and the feeling of security which the patient receives upon visiting a physician The psychic factors control many of the organic or functional disturbances wherein there is a reverse relationship in that many of the latter symptoms induce psychic changes It is well for the physician to realize that many of the changes in these patients are not imaginary,' but that they have a definite origin and effect so that the understanding and sympathy of the physician for his patient is of the most vital importance in the treatment of this condition A physician who underestimates this feature is bound to give imperfect treatment

Medical Treatment The medical treatment of the menopause is much like that of any condition which involves an individual who is unstable irritable over anxious and uncomfortable In a considerable number of patients sedation with the barbiturates is of sufficient aid so that no further treatment is necessary These patients are usually suffering from a rather mild condition and simple reassurance by the physician plus sedation, will reduce their irritability and also control some of the minor vascular and nervous changes such as flushes sweats and so forth Often these people have associated hypertension which must be treated in the orthodox manner Furthermore the complications of hypertension such as cardiac and kidney disease must also be handled Diabetes which may be coincidental with the menopause is also a medical problem and should be treated in accordance with the usual methods Nevertheless it is not unusual that the proper and complete treatment of the menopausal symptoms may diminish the intensity of the diabetic state, especially in those cases which make their appearance during the menopause

Psychologic Treatment The psychologic treatment of the menopause cannot be underestimated The individuals must be assured that their condition is not hopeless, since many of them feel it to be a sign of weak constitution or of old age and debility Many women feel that their feminity and sexual activity have departed, that they are relegated to an empty life, that they have lost their physical attraction These women must be told that there is no need for thoughts of such nature, that they are entering upon a phase of life which may hold more happiness for them than at any other time that their mental activities may improve with the diminished distractions from raising children and attaining economic security In the more severe cases it is possible that a specialized psychotherapy might be necessary to aid the patient An understanding of the psychologic traits of women their vanities and designs will be of great value Potent suggestion without any other agent is often effective in this regard The author has seen a number of cases wherein hypnosis has acted dramatically in relieving all symptoms of the menopause Such treatment is not necessarily recommended but it gives an insight into the role that suggestion may play in the treatment of the menopause

Endocrine Treatment The endocrine therapy of the menopause is probably one of the brightest chapters in recent medical therapeutics It has been so perfected that practically all cases may be satisfactorily treated by any physician who has an under

Miscellaneous Conditions

PREMENSTRUAL TENSION

This condition is most common and occurs to varying degrees in about 40 per cent of regularly menstruating women Chief symptoms are irritability, emotional instability, fatigue, depression, excitability, headache, tension of the skeletal muscles, and either increased or decreased appetite The signs are chiefly limited to bloating of the abdomen and edema of various tissues There is also an aggravation of disturbances *which the patient coincidentally possesses* such as allergies, dermatoses arthritis, etc The discomfort of these patients may be considerable The social maladjustments are often quite intense and much harm to domestic relationships may result There is undoubtedly a great economic loss due to the inefficiency of workers at this time of the month

These symptoms and signs may be explained by the sodium and fluid retention associated with the increased level of estrogens during the week or so preceding the menstrual period Various tissues swell under this influence giving rise to the respective symptoms *The treatment consists* of restricting salt intake for about ten days before the onset of menstruation and the antagonization of the endogenous estrogens by androgens Thus, 25 mg of testosterone propionate injected one week before the menses will relieve most cases Methyl testosterone administered orally in 10 mg doses starting seven days before the onset will also give excellent results Occasionally it is desirable to administer ammonium chloride in the usual doses if considerable edema occurs at this time

Painful Breasts

*It is rather common for women to com*plain of tender engorged breasts for several days before the onset of menstruation This may be exaggerated in some giving rise to the condition called chronic cystic mastitis or mastodynia The ducts become hyperplastic and form retention cysts the distention of which may be quite painful This condition responds well to androgens either injections of 25 mg of testosterone propionate twice weekly until tenderness subsides or methyl testosterone, 10 mg daily until the same results are achieved A second course may be given the following month Patients are usually free of dis*comfort for long periods of time* after such therapy If there is a recurrence of the condition, a second course of therapy may be given

the result of fluid retention in the tissue as part of the physiologic effect of estrogen administration These symptoms are similar in character to those which appear in the premenstrual phase in which sudden rise of the estrogen level is also encountered When toxic results are obtained, lowering the dosage will often prevent a recurrence Otherwise if toxic results occur below the therapeutic level of the estrogen dose, it is well to abandon oral therapy and commence the injections of the more slowly absorbed estrogens

Other complications of estrogen therapy are the development of painful breasts and uterine bleeding The development of painful breasts in the menstruating woman is also a physiologic effect since breast tissue is responsive to estrogens This condition may be relieved in two ways either by the cessation of estrogen therapy for a time and its renewal at lower dosages or else by the administration of androgens such as testosterone propionate which antagonize the effect of the estrogens Uterine bleeding is commonly encountered with the more rapidly absorbed estrogens such as the free hormones either by injection or by mouth and especially by diethylstilbestrol

Some patients will have a bleeding episode rather early in the course of treatment others only after prolonged treatment This bleeding is similar to the estrogen deprivation bleeding and is anovulatory in character As a rule this bleeding is relatively scant but at times may be rather profuse and alarming The patient should be treated in the latter case by withdrawal of estrogen completely and if the bleeding continues over an undesirable period of time androgens may be administered to suppress this flow The dosage of testosterone propionate in such cases should be approximately 25 mg daily until bleeding stops Diethylstilbestrol is most prone to induce bleeding and a change to another estrogen is advocated in those women who have a tendency to bleed

In about 5 to 10 per cent of patients one encounters an allergic reaction to the oil solution injected This may be simply an itching indurated area about the needle site but may also cause marked edema of the tissues over quite a large area and cause considerable distress A generalized dermatitis is also rarely seen It is suggested that a preparation containing another kind of vegetable oil be substituted or aqueous suspensions be employed since these are nonallergic

Other uncommon but not rare complications of the menopause are those which follow the atrophy of the epithelium of the vagina and vulva In the former instance senile vaginitis develops in which the mucous membrane becomes thin and friable leading to bleeding inflammation and secondary infection This condition responds readily to estrogen therapy either administered systemically or applied locally in the form of suppositories or even tablets designed for oral use inserted at fairly regular intervals such as two or three times weekly Kraurosis vulvae is a serious disorder considered precancerous by many It is resistant to estrogen therapy although high doses have been beneficial in some cases Surgical excision is advocated where estrogen therapy fails Dermatitis of the vulva either eczematous or inflammatory is also partially relieved by estrogens Whether the estrogens act specifically on this condition or relieve the nervous tension which may be the primary cause of this condition is still an open question Ointments or creams containing estrogens should be applied If the condition is the result of an estrogen deficiency prompt relief should be obtained and maintained as long as therapy is continued If the condition is refractory to this treatment the dermatosis may be considered primarily neurogenic

come Increasing duration of the disease seems to be associated with decreasing last ing remission

Other Antithyroid Drugs Treatment of hyperthyroidism with *methylthiouracil* achieves comparable results but the toxicity of the drug is greater *Methimazole* is a highly potent antithyroid drug the dose ranges from 5 to 10 mg every eight hours Although the experience with this drug is not sufficiently great to make exact com parisons with propylthiouracil in regard to toxicity, it is tolerated in some patients in whom propylthiouracil is not and its relationship to propylthiouracil in regard to general use remains to be defined

More recently *5 iodo 2 thiouracil* has be introduced to test the hypotheses th greater concentration of the drug in tl thyroid gland may result from iodinatic and that an antithyroid agent which is n *goitrogenic* might result Some of the ev dence indicates that the compound d pends largely on its iodine content for i effect in hyperthyroidism and the fact th neither radioactive iodine uptake studi nor protein bound iodine values are rel able indices in its presence render difficu an early assessment of its effect and a mor general experience will be required befor the place of this type of substance can b ascertained

Myxedema

MYXEDEMA is caused by a deficiency or *complete absence of thyroid function It* occurs spontaneously at any age usually in association with profound regressive changes in the thyroid gland Myxedema is a common complication of surgical opera tions on the thyroid gland may occur after the use of radioiodine for hyperthyroidism and may follow chronic thyroiditis Rever sible myxedema can occur in goitrous pa tients when the goitrogenic influence what ever it may be is extreme this condition may be seen after the prolonged ingestion of antithyroid compounds

TREATMENT

The administration of thyroid is a spe cific treatment for myxedema Unlike the *hormone of any other* endocrine gland the thyroid hormone is fully effective when the whole gland is given by mouth and other routes of administration do not offer any advantages Although pure thyroxin from natural sources and of synthetic origin is available it does not have any advantages over thyroid U S P in therapy

Thyroxin is practically insoluble in wate *except in strongly alkaline solutions an* absorption from the gastrointestinal trac is uncertain *Thyroid*, the dried defatted powder from the thyroid glands of slaugl ter house animals contains the thyroic hormone in a form which is readily assim ilated Various other types of thyroid prep aration are advertised for therapeutic purposes such as concentrates of thyroglo bulin thyroid in strengths other than tha specified in the U S P thyroxine peptides salts of thyroxine, and preparations of iodinated proteins but none is superior to thyroid U S P which has the additional advantages of uniformity and economy

The required daily dose of thyroid varies within narrow limits Less than 60 mg daily is seldom sufficient and more than 0 2 Gm is rarely required Most patients with myxedema do well with 90–120 mg daily Young people may need more while the elderly require less indeed the *smallest* dose compatible with comfort is the best dose for old people There does not appear to be any need for dividing the daily dose

29. *Diseases of the Thyroid*

E. B. ASTWOOD

& W P VANDER LAAN

Hyperthyroidism

ALTHOUGH the cause of hyperthyroidism is unknown all of its clinical manifestations except the thyroid enlargement and the ocular changes are mediated by the excessive production of thyroid hormone Current therapy is directed toward reducing the endocrine activity of the thyroid gland the primary disturbance which gives rise to thyrotoxicosis cannot at present be attacked Hyperthyroidism is associated with various degrees of thyroid enlargement the gland may be evenly enlarged or it may contain one or more nodules of varying size However the physical appearance of the thyroid has little bearing on the treatment of the disease

TREATMENT

Hyperthyroidism is now treated in several different ways The four common therapeutic measures include iodine subtotal thyroidectomy radioiodine and antithyroid drugs employed singly or in various combinations At present the use of iodine alone and iodine followed by subtotal thyroidectomy depends largely on established custom

Iodine

Iodine alone often is incompletely effective in hyperthyroidism Patients with mild hyperthyroidism sometimes respond favorably if iodine therapy is continued almost indefinitely but often the immediate favorable response is followed by a slow return of the original intensity of hyperthyroidism When this occurs a serious therapeutic problem is presented Such iodine refractory patients cannot be treated by operation radioiodine cannot be used until the iodine has been withdrawn for some weeks and prolonged antithyroid therapy may be necessary before the thyrotoxicosis is controlled Iodine then does not appear to have a place in the treatment of hyperthyroidism unless an operation is contemplated

Subtotal Thyroidectomy

With rare exceptions subtotal thyroidectomy does not have advantage over radioiodine as a treatment Indeed radioiodine accomplishes all that can be obtained with surgery without the discomfort and risk and without damage to the parathyroid glands

plished by adding potassium iodide to the commercial supplies of common salt, and in the United States the quantity added is 0 01 per cent This would provide *several times* the amount estimated to be *required if* 5–10 Gm of salt are consumed daily While added iodine may greatly reduce the inci dence of goiter, it does not eliminate the disorder, other more effective measures need to be investigated

TREATMENT

Although iodine deficiency is a common cause of goiter, iodine is not an efficient remedy for the condition Goiter due to *antithyroid* compounds is not materially *benefited* by iodine, and it is a common clinical experience that its administration is often without effect upon the goiters encountered in nonendemic regions Iodine may actually be dangerous and in iodine deficient regions at least it sometimes gives rise to *Jod Basedow* or iodine induced hyperthyroidism

Thyroid is the most effective remedy for simple goiter Regardless of the cause of goiter, the actual enlargement is probably a compensatory phenomenon, some factor, such as iodine deficiency an antithyroid compound, thiocyanate ion or some still unknown influence prevents normal thy roid function and the gland enlarges to meet the need for thyroid hormone The administration of thyroid relieves the gland *from its responsibility* of manufac *the hormone*, and the consequence roid *atrophy*

Goiter of recent origin usually *promptly* when thyroid in a d 0 12–0 25 Gm daily is *administered* advisable to begin *treatment with* 0 daily, if after a month a *change* detectable, the dose *should be increa* 0 2 Gm, and later to 0 25 Gm if nec *Treatment should* be continued un *maximal* regression has been obtaine advisable to continue *treatment* smaller dose of *06–0 12 Gm daily* for *six months thereafter If an effect* achieved from 0 25 Gm daily given least six months nothing is likely gained from further treatment or larger doses Goiters of long sta usually do not respond Although enlargements of recent origin are mo ily treated, single large nodules respond well if treatment is given the active phase of growth

Should the goiter or the nodule co to enlarge during thyroid therapy, three possibilities should be consi the patient may have hyperthyroid thyroiditis or the *thyroid may be th* of a neoplasm *which requires surgic* tervention In the latter instance, th ministration of thyroid can serve therapeutic test if there is doubt co ing diagnosis

Thyroiditis

THE acute and subacute forms are prob ably variants of the same disease and are characterized by a painful tender swelling of the gland associated with fever and its constitutional symptoms The inflamma tory process may involve the entire thyroid at once or it may spread slowly The dis ease may be severe and last for only a period, or it may be milder and con with exacerbations and partial remi for several months This *variation* difficult the evaluation of any for therapy There is not any form of th that has been proved specific and

Cretinism and Childhood Myxedema

IN REGIONS where goiter is common the goitrogenic influence may be so extreme that thyroid function is seriously impaired from the time of birth Endemic cretinism, often in association with goiter, is the result More rarely the thyroid gland may be absent or undeveloped at birth resulting in so-called sporadic cretinism Deficient thyroid function arising later in childhood causes a clinical syndrome with features of both cretinism and adult myxedema

TREATMENT

As in myxedema of the adult thyroid is a specific treatment in cretinism and childhood myxedema Prompt diagnosis and optimal dosage are more important in childhood the younger the child the more urgent the treatment Mental development is permanently and irreversibly impaired if treatment is not given early and continued in optimal dose until puberty Even when treatment is begun in infancy mental deficiency is common in cretinous persons Some believe this is due to an associated congenital abnormality of cerebral development Inadequate dosage is another possibility Mental development is so important that continued overdosage with thyroid is entirely justified in cretins during infancy and early childhood

The dosage of thyroid is determined by trial and should be the largest that can be given without causing undue irritability, diarrhea hyperthermia or discomfort The mother and family should be coached in the importance of uninterrupted treatment Infants should receive 60 mg daily, and frequent attempts to increase the daily dosage should be made as the child grows older If diarrhea vomiting excessive weight loss or irritability occur therapy should be omitted for a few days and then resumed with a slightly smaller dose

The mental deficiency of untreated cretinism often requires institutional care In this advanced stage of the disease, thyroid will not correct the idiocy even though it will still reverse the physical signs of myxedema and induce extensive physical development Some custodians of mentally undeveloped cretins prefer to withhold thyroid as its use causes their charges to become irritable and more difficult to manage

Nontoxic Goiter

SIMPLE enlargement is the commonest disorder of the thyroid gland It occurs in all parts of the world although the incidence varies widely in different regions Goiter is more frequent in females and often is first noticed at puberty or during pregnancy The enlargement may be uniform or uneven and the goiter may consist of single or multiple nodules the nodules being more frequent in the larger and older goiters The etiology is incompletely understood although iodine deficiency is a well-established factor, and antithyroid compounds in the diet may be a second factor

PROPHYLAXIS

The only preventive measure of proved effectiveness is an increased intake of iodine This is most commonly accom

30. Diseases of the Adrenal

PAUL L WERMER

THE adrenal gland possesses two functioning hormonal divisions the cortex and the medulla Each plays a role in assisting the adjustment of the organism to stress situations yet their secretions are not stimulated by the same mechanisms The adrenal medulla responds by pouring epinephrine and norepinephrine into the blood stream during emotional stress or when potential danger threatens from the internal or external environment Thus the medulla releases its secretion chiefly during emergency situations The cortex on the other hand is concerned with many homeostatic mechanisms and therefore maintains a steady release of corticosteroids to aid in establishing a constant *milieu intérieur* Nevertheless it is obvious that the cortex plays a most important role in the adaptation of the organism to stress This is strikingly demonstrated following experimental extirpation of the adrenal cortex in animals or in Addison's disease where minor stresses are often followed by a fulminating sequence of events (adrenal crisis) which lead to death even though the adrenal medulla is intact Therefore any hypothesis for adrenal function must explain the ability of the adrenal cortex to respond quickly to stress and to accelerate its output of steroid hormones on physiologic demand The most widely accepted theory postulates that (1) release of epinephrine and norepinephrine stimulates centers in the hypothalamus (2) these in turn stimulate the anterior pituitary to release the pituitary adrenocorticotropic hormone (corticotropin) and (3) corticotropin release stimulates the adrenal cortex to greater activity

The exact mechanism by which the hypothalamic centers stimulate the pituitary has not been explained satisfactorily It is evidently not a neural pathway since severance of all neural connections to the anterior pituitary in experimental animals made no discernible change in the pituitary response to epinephrine injection or alarming stimuli

Although our knowledge is still meager it is interesting to speculate that so intimately associated structures as the medulla and cortex of the adrenal apparently require the intermediation of the pituitary to act in concert

doubtful that any treatment is uniformly effective Sulfonamides and antibiotics have been tried with only occasional success Thiouracil and its derivatives have been claimed to be highly effective but in some instances benefit is not observed, a rationale for thiouracil therapy has not yet been suggested The use of roentgen irradiation often has proved successful when administered in small doses of 600–800 r Improvement after irradiation is often observed in a few days in fact most patients are well in six weeks However the natural course of the disease may be responsible for the improvement noticed in some instances

Chronic Thyroiditis Chronic thyroiditis of the Hashimoto type (struma lymphomatosa) or of Riedel s variety (struma ligneosa) usually is not diagnosed correctly clinically and little is known of the cause or cure The hardness of the goiter may suggest carcinoma, and diagnosis is usually made at the time of operation The failure of a goiter to respond to the administration of thyroid and the symmetrical nature of the thyroid enlargement might suggest a diagnosis of chronic thyroiditis

Roentgen ray therapy has sometimes been effective in the lymphoid type of chronic thyroiditis Operative intervention may be needed in Riedel s type if tracheal compression occurs

TABLE 28 SUMMARY OF EFFECTS OF ADRENAL INSUFFICIENCY

Electrolyte and water metabolism	*Carbohydrate metabolism*	*Fat metabolism*	*Protein metabolism*	*Lymphoid tissue*	*Skin pigmentation*	*Sexual hair muscula strength*
Renal excretion of sodium chloride water Retention of potassium Hemoconcentration Decreased serum sodium and chloride Increased serum potassium hypotension weight loss Late—diminished ability to excrete water	Gluconeogenesis decreases Insulin effect enhanced Peripheral utilization of glucose increased Low fasting blood sugar Liver glycogen depletion	Increased fat utilization Decrease in fat depots Decrease in liver fat	Decreased conversion of protein to glucose	Generalized lymphoid hyperplasia Increase in circulating eosinophil count	Increased melanin deposition in skin and mucous membranes areas of vitiligo	Decreased sexual hair Decreased muscle strength

genic steroids Table 28 summarizes these various effects

Dissociation of these various metabolic control mechanisms often occurs in adrenocortical disease thus the predominant symptoms of the patient might be referable solely to one or to combinations of carbohydrate fat or electrolyte imbalance in varying degrees On the other hand, disturbance of all factors may occur in profound Addison s disease

THE ADRENAL HORMONES

Recent chromatographic studies seem to indicate that the six adrenal steroids listed below predominate in the venous return flow from human adrenal glands or are excreted in the urine A similar group of hormones has been isolated from hog adrenal brie These findings have led some investigators to suggest that the other twenty or so adrenal steroids reported isolated may be metabolic degradation products of the six hormones This view is not accepted generally and many authorities believe that androgenic adrenocortical steroids are normally secreted

1 *Hydrocortisone* (Compound F) an *11 17, oxysteroid*, is the chief component found It has the ability to maintain life in adrenalectomized animals and to protect them against stress situations It promotes gluconeogenesis and the mobilization of fat from the liver and fat depots and possesses lymphoid and eosinophil regulating powers but has little electrolyte regulatory capacity

2 *Cortisone* (Compound E) also an 11 17 oxysteroid resembles hydrocortisone in activity

3 *Corticosterone* (Compound B) is another 11 17 oxysteroid isolated in smaller quantity It is generally less active than cortisone or hydrocortisone but possesses better electrolyte regulatory powers

4 *11 Dehydrocorticosterone* (Compound A) possesses more sodium and chloride

Dysfunction of the Adrenal Cortex

THE adrenal cortex mediates the adaptation of the organism to specific and nonspecific stress by numerous metabolic mechanisms Under or over function of the adrenal cortex alters the ability of the organism to respond to stress situations by changes in these metabolic protective mechanisms In addition the adrenal cortex in coordination with the anterior pituitary gonads and thyroid maintains an output of hormones to secure a constant internal environment for the body cells To treat adrenocortical disease an understanding of its physiology is mandatory

PHYSIOLOGY

When the adrenal glands are extirpated in the experimental animal an almost immediate and striking increase occurs in the renal excretion of sodium chloride and water whereas renal potassium excretion is decreased A consequence of this change in electrolyte and water balance is dehydration hemoconcentration decreased serum concentration of sodium chloride increased serum potassium level hypotension and weight loss

Although initially a great deal of water is lost from the system once balance is established the animal becomes peculiarly sensitive to water Water diuresis is greatly diminished in animals with extirpated adrenals and temporary hemodilution will follow the injection of quantities of water This effect is probably due to an unopposed rise in the antidiuretic principle of the posterior pituitary gland Normally the adrenal cortex exists in equilibrium with the antidiuretic principle of the posterior pituitary gland and acts with it to exert control over water and electrolyte absorption by the kidney tubule

Profound alterations in carbohydrate metabolism also occur The rate of conversion of proteins to carbohydrates (gluconeogenesis) decreases The inhibitory effect of anterior pituitary extracts on enzyme processes concerned with the peripheral utilization of glucose is decreased Insulin effect is thereby increased resulting in depletion of peripheral glucose and liver glycogen reserves with low fasting blood sugar values

An increased utilization of fat occurs—probably to compensate for the loss of protein as an energy source—so that stored fat in the liver and in the fat depots is decreased

Apparently the adrenal cortex and lymphoid tissue in the body also exist in equilibrium because following removal of the adrenals a generalized lymphoid hyperplasia occurs The circulating eosinophil count also increases with adrenal insufficiency

The adrenals and the anterior pituitary play a role in the control of human skin pigmentation for in patients with Addison s disease but with intact anterior pituitary function a characteristic bronzing occurs The hyperpigmentation is due to an increased mobilization of melanin to the skin and mucous membranes Vitiligo is another variation in pigment control encountered in Addison s disease Such pigmentary changes do not occur in secondary failure of the adrenal cortex due to pituitary hypofunction

In man growth of sexual hair and the development of the skeletal musculature are also partially under adrenocortical control since patients with Addison's disease frequently show extremely scanty sexual hair and marked asthenia These effects are probably caused by lack of certain andro-

forms Cortisone may be obtained as tablets pellets and a microcrystalline suspension They possess excellent carbohydrate and some electrolyte regulating capacity

Desoxycorticosterone Acetate (DCA) This steroid is available in oil solutions containing 5 mg per cc of solution or as pellets of 75 or 125 mg It possesses excellent electrolyte regulating capacity but exerts practically no effect on other metabolic regulating mechanisms

Epinephrine This is one of the hormones of the adrenal medulla It is valuable to combat hypotension and shock It is available as (1) a 1 1000 aqueous solution with a usual dose of 0 2 cc intravenously or 0 5 cc intramuscularly and (2) a 1 500 oil solution with an average dose of 0 5 cc intramuscularly The aqueous solution is more rapidly utilized and is indicated in emergency the oil solution for sustained effect

Acute adrenocortical insufficiency of any etiology is a medical emergency which must be treated promptly if the patient is to survive Main reliance is placed upon aqueous adrenocortical extract because it is the most rapidly utilized form of substitution therapy Intravenous fluids including fresh blood and plasma and epinephrine hydrochloride are also of great value but should be reserved for specific indications Lipo adrenal extract cortisone and desoxycorticosterone are absorbed and utilized more slowly than the aqueous extract and are used as adjunctive therapy during acute critical periods but become important during the more chronic phases of treatment

Waterhouse Friderichsen Syndrome

Possibly the most severe adrenocortical crisis encountered clinically is the Waterhouse Friderichsen syndrome In the newborn child the syndrome is usually associated with bilateral hemorrhages into drenal gland with resultant acute

The condition also occurs later in li in young adults, chiefly of the military ag and usually is associated with either meningococcus or staphylococcus septice mia • It is essential to suspect Waterhouse Friderichsen syndrome in any patient with meningococcemia or staphylococcemia who shows sudden cyanosis, purpuric manifesta tions, and shock despite an initial and satisfactory response to antibiotic therapy The purpuric manifestations appear on all external surfaces and coalesce rapidly so that the lesions look like hemorrhages into the skin Shock is profound and striking resembling that seen in an overwhelming systemic infection If the patient is to be saved, it is important to institute massiv adrenocortical substitution therapy almo immediately

Treatment Immediate adrenocorti hormone therapy of the substitution t should be instituted by massive doses aqueous adrenocortical extract, 30–50 intravenously and 10 cc intramuscul Intravenous fluids possibly plasma fresh blood and continuous specific bacterial therapy also should be ad tered If vascular collapse is a pron symptom epinephrine hydrochlori cc of a 1 1000 aqueous solution sho given subcutaneously or 0 2 cc ma jected intravenously Subsequently of epinephrine in oil 1 500 may be intramuscularly every eight hour systolic blood pressure neverthele below 80 mm Hg 100–150 cc of adrenocortical extract should be a plasma glucose saline solution by a continuous intravenous inf ing the first few hours after d been established This should by 10 cc of aqueous adrenocor intramuscularly every hour the clinical improvement is ma preparation of the plasma mixture, the aqueous adrenoc

• See also Chapter 6

retaining capacity but less carbohydrate, protein, and fat regulatory power than corticosterone

5 *17 - Hydroxy - 11 - desoxycorticosterone* (Compound S) is inactive in carbohydrate and protein metabolism but exhibits influence on muscle strength

6 *11 Desoxycorticosterone* has the greatest electrolyte regulatory power but minimal capacity in other control mechanisms

Metabolic degradation products may include the androgenic steroids responsible for certain adrenocortical derangements

Diseases of the Adrenal Gland

THE diseases of the adrenal gland which are recognized clinically fall into three categories (1) hypofunction of the adrenal cortex, (2) hyperfunction of the adrenal cortex, and (3) hyperfunction of the adrenal medulla

No clinical state associated with hypofunction of the adrenal medulla has been described

ACUTE ADRENOCORTICAL HYPOFUNCTION

Acute adrenocortical hypofunction or adrenal crisis may be classified as follows

1 Waterhouse Friderichsen syndrome,
2 Addisonian crisis
3 Surgical
   a Surgery of the adrenal glands
   b Surgery or trauma in patients with potential adrenocortical insufficiency

Available Therapeutic Agents

The following adrenocortical preparations are available for therapeutic purposes in the treatment of adrenocortical hypofunction

Sodium Chloride Loeb demonstrated several decades ago that some patients with Addison s disease might be maintained with salt alone Today, salt is regarded as an adjunctive to hormonal therapy, since it corrects only salt imbalance and not the other metabolic disturbances associated with adrenal hypofunction

Corticotropin (ACTH) This material contains the specific anterior pituitary adrenocorticotropic factor It can only be used if intact adrenal cortices are present as in secondary adrenocortical hypofunction or in preparation for adrenal surgery It is biologically standardized in U S P units one unit containing the specific adrenocorticotropic activity of 1 mg of the International Standard

Adrenocortical Extracts These are of two types (1) The aqueous extract (ACE) derived from beef adrenals most valuable of all preparations for emergency use since it is quickly utilized Peak effect is attained one to two hours after intramuscular injection with a total duration of effect of approximately six to eight hours It may be injected intramuscularly or intravenously These extracts are standardized biologically against known quantities of cortisone (2) The oil extract (lipo-adrenal extract) prepared from hog adrenals and dissolved in oil This preparation is approximately ten times as potent as the aqueous extract, is slower in absorption and must be injected intramuscularly Peak effect is attained in four to six hours with a total duration of eight to twelve hours It possesses superior carbohydrate regulating capacity

Cortisone (Compound E) and Hydrocortisone (Compound F) These synthetic 11 17 oxysteroids are available in various

kept in bed in shock position, well covered to prevent chilling, and should be disturbed as little as possible, but the blood pressure, pulse, respiration, and rectal temperature should be charted every hour Therapy should begin immediately with rapidly utilizable aqueous adrenocortical extract, 30–50 cc intravenously and 10 cc intramuscularly, followed by 5–10 cc intramuscularly *every hour* As the patient improves, the interval of administration *should be increased to two and later to* three hours

Lipo adrenocortical extract, 0 5–1 cc every six to eight hours, may be substituted for the aqueous preparation after the patient has responded Cortisone acetate, 0 2 Gm, may be given in four divided doses on the first day, 0 1 Gm on the next, and 50 mg thereafter until appetite and food intake are normal With cortisone acetate therapy, intravenous glucose administration may be necessary only initially

Epinephrine hypochloride, 0 3–0 5 cc. of a 1 1000 aqueous solution, is given subcutaneously if the systolic blood pressure is below 80 mm Hg This may be followed in an hour by 0 5 cc of *epinephrine in oil* 1 500

At the onset of therapy 10–20 mg of desoxycorticosterone acetate in oil is injected intramuscularly to enhance salt and water retention and to aid potassium excretion The total dose should be divided and given in two or three sites to hasten absorption Thereafter, 5 mg may be given daily depending upon the state of hydration (signs of edema, sudden increase in weight, and change in blood pressure are danger signals)

As soon as possible after diagnosis, 250 cc of plasma or concentrated human albumin, 25 Gm in 5 per cent solution, is given *intravenously* To this infusion may be added 30 cc of aqueous adrenocortical extract, the specific chemotherapeutic agent, and 250 cc of 10 per cent glucose in normal saline solution The rate of administration varies with the intensity of the need but should not be less than 100 drops a minute There should be no hesitancy in repeating this infusion if the condition of the patient has not materially improved. When the patient has improved, an infusion of 1000 cc of 10 per cent glucose with the chemotherapeutic agent may be used thereafter Parenteral fluid intake, while vital, should not be permitted to exceed 3500 cc *during the first twenty four-hour* period of treatment Chemotherapy should be continued for at least two days or until definite clinical improvement occurs

Fever may be controlled by the usual antipyretics, but the salicylates are contraindicated if the patient has a low or falling blood pressure, as they may stimulate vasodilatation After twelve to twenty four hours, small quantities of carbonated beverages or sweetened fruit juice may be tolerated at hourly or two-hourly intervals Food intake is gradually increased as the patient improves

One must guard against edema which may appear after a period of temporary *improvement since it reflects development* of overhydration The edema may be (1) cerebral, with loss of consciousness (2) pulmonary, with or without signs of cardiac failure or (3) peripheral involving the extremities Presence of edema requires immediate reduction in the administration of parenteral *fluid* especially *normal saline* solution the discontinuance of desoxycorticosterone acetate, and an increase in aqueous adrenocortical extract to 10 cc intramuscularly every two *to three hours* or 50 mg of cortisone intramuscularly every six hours One to three units of plasma or 25–50 Gm of concentrated human serum albumin administered slowly by vein will help combat edema

After forty-eight hours of treatment the temperature should approach normal and the clinical status of the patient should be

should be added to a unit of plasma and then 10 per cent glucose in normal saline may be added up to 1500 cc This solution should be administered slowly over the first two to four hours, the rate of administration being determined by the condition of the patient

To combat hemoconcentration, a transfusion of fresh blood should be administered as quickly as possible

Desoxycorticosterone acetate should be administered in doses of 15 mg immediately after the initial aqueous adrenocortical extract This is followed by 5 mg within twelve hours if the blood pressure remains low Desoxycorticosterone treatment will combat the loss of sodium and chloride and will permit excretion of potassium thus tending to overcome the electrolyte imbalance

Cortisone acetate in 0 1 Gm doses should be given daily for the first few days after the diagnosis has been established This aids in the re establishment of proper gluconeogenesis

Specific antibiotic therapy to combat the infection should be continued preferably intravenously and in large doses

When the patient has improved the interval of administration of the aqueous adrenocortical extract may be increased to two and later to every three hours As the patient s fever subsides and appetite improves lipo adrenocortical extract may be substituted for the aqueous preparation in doses of 0 5–1 cc intramuscularly every six to eight hours As the signs and symptoms of the responsible infection subside and blood cultures become negative the adrenocortical supportive therapy may be withdrawn gradually and cautiously over a period of several days

Addisonian Crisis

Addisonian crisis is a form of acute adrenocortical insufficiency which may occur suddenly in a patient with Addison's disease due to the imposition of some sudden stress, such as an infection A somewhat similar syndrome occurs in patients following extirpation of adrenal tissue, or in patients with a covert adrenocortical insufficiency following an acute stress situation such as trauma or surgery

Whatever the cause, the symptoms and signs include nausea, vomiting, dehydration hypotension, a feeble pulse, disorientation, coma vascular collapse, and usually subnormal temperature However, temperature changes do tend to vary with the cause and course of adrenal crisis Terminally, and during substitution treatment, hyperpyrexia may occur If crisis is precipitated by surgical removal of adrenal tissue, hyperpyrexia frequently develops following the operation together with signs of severe shock In the form of crisis following surgery or trauma in patients with potential adrenocortical insufficiency hyperpyrexia and the other signs and symptoms may be delayed for twelve to forty-eight hours after the traumatic incident When dehydration occurs, it tends to enhance existing changes in skin pigmentation

Treatment The treatment of Addisonian crisis occurring in a previously untreated patient varies from that of the patient being treated with desoxycorticosterone acetate The primary disturbance in treated patients usually is a hypoglycemia as electrolyte imbalance seldom occurs In the untreated patient, however, both electrolyte imbalance and hypoglycemia usually ensue

Untreated Addison's Disease The previously untreated Addisonian patient in acute adrenal crisis requires immediate substitution therapy to correct the hypoglycemia and to combat further electrolyte imbalance and water loss Fluids and sodium chloride also must be furnished to overcome the dehydration and shock If infection is present specific chemotherapy is also indicated The patient should be

injection of 25 units of corticotropin four times daily This will stimulate the cortex of the unaffected gland (if tumor is unilateral) or help inaugurate secretion in hypoplastic areas

The day before operation 5 cc of aqueous adrenocortical extract is given intramuscularly every four hours and 10 mg of desoxycorticosterone acetate in oil is also administered

Just before operation an intravenous infusion should be begun containing 500 cc of 10 per cent glucose in isotonic saline solution and 25 cc of aqueous adrenal extract This infusion should be completed before anesthesia It should be followed during operation by continuous infusion of similar nature containing at least 10 cc of aqueous adrenocortical extract to 100 cc of solution and 250–500 cc of plasma Plasma or whole blood should be available to counteract sudden drop in blood pressure due to blood loss Epinephrine may be used for control of blood pressure drop due to other causes

Thorn interdicts the use of morphine or avertin' and advises use of smaller doses of all drugs than routine

Postoperatively the corticotropin should be maintained for approximately seventy two hours Should postoperative acute *adrenocortical failure* appear it usually is presaged by an acute rise in temperature followed by shock The treatment is the same as for adrenal crisis occurring following trauma in patients with covert adrenocortical function

Treatment of Adrenal Crisis Following Trauma in Covert Hypoadrenocorticalism Symptoms of profound shock and hyperpyrexia usually appear twenty four to forty eight hours after the traumatic experience in covert hypoadrenocorticalism The cardinal signs and symptoms of adrenal crisis are present but shock predominates If marked hypotension and vascular collapse are present epinephrine 0 2 cc of a 1 1000 aqueous solution may be given intravenously or, if less urgent 0 5 cc intramuscularly To sustain the blood pressure 0 5 cc of *epinephrine in oil* (1 500) should be administered intramuscularly every eight hours while the systolic blood pressure is below 80 mm Hg Whole blood or plasma transfusions should be used to combat shock

During the first two or three hours a glucose saline plasma solution containing 100–150 cc of aqueous adrenocortical extract similar to that described for the treatment of Addisonian crisis should be given by intravenous infusion Aqueous extract, 10 cc, is administered every hour thereafter until the patient is out of danger

Desoxycorticosterone acetate, 15 mg should be administered as soon as possible followed by 5 mg within twelve hours if the blood pressure remains low This dose may be repeated at twenty four-hour intervals if the hypofunction persists All therapy should be gradually withdrawn in patients following adrenal surgery but continued therapy may be necessary for covert cortical hypofunction—as outlined for chronic adrenocortical insufficiency

CHRONIC ADRENOCORTICAL HYPOFUNCTION

Chronic adrenocortical hypofunction may vary in degree from slight to absolute cessation of function The hypofunction may be apparent in only one of the homeostatic mechanisms partially controlled by the cortex or it may affect all of them in varying or equal degree To add to the complexity of the diagnostic situation the cortical hypofunction may be primary—due to disease of the adrenal cortex—or secondary—due to malfunction of the anterior pituitary gland

Regardless of cause chronic adrenocortical insufficiency requires substitution therapy although corticotropin (stimula

much improved When the patient becomes asymptomatic has a normal blood sugar, and seems to be well hydrated the aqueous adrenocortical extract or lipo adrenocortical extract may be gradually withdrawn Simultaneously a maintenance regimen to control the underlying Addison s disease must be inaugurated as outlined under chronic adrenocortical insufficiency

Previously Treated Addison s Disease Patients with Addison s disease maintained on desoxycorticosterone acetate may develop adrenal crisis following the onset of acute infection or gastrointestinal upset The suddenly increased hormone requirement imposed by such a stress situation probably precipitates the crisis Hypoglycemic manifestations predominate because desoxycorticosterone acetate does not possess satisfactory carbohydrate metabolism regulatory capacity The primary objective of treatment is to overcome the hypoglycemia but fluids and sodium chloride also must be provided The vital nutritional requirements must be maintained and desoxycorticosterone acetate intoxication guarded against Again chief reliance is placed on aqueous adrenocortical extract 30–50 cc should be administered intravenously immediately upon making the diagnosis and 5 cc should be administered intramuscularly every hour until improvement occurs Thereafter the intervals of treatment are lengthened as previously indicated Cortisone acetate in 25–50 mg doses intramuscularly every six hours is valuable auxiliary treatment Intravenous fluids should be restricted to only 1000 cc of 10 per cent glucose in normal saline during the first twelve hours This may be repeated during the second twelve hours if the intake of fluids by mouth is not well tolerated Human serum albumin 25–50 Gm or 250–500 cc. of plasma may be given intravenously to combat shock to prevent water intoxication and to provide a source of readily assimilated protein Plasma or albumin may be added to the glucose saline solution

Patients on desoxycorticosterone therapy frequently have a potassium lack If serum potassium determinations are low and the electrocardiogram shows the characteristic changes of hypopotassemia * a concentrated solution of 2 Gm of potassium acid phosphate and 0 4 Gm of potassium bi acid phosphate should be added to an infusion of 10 per cent glucose in water If renal insufficiency is also present potassium is definitely contraindicated

When infection is the precipitating cause specific antibiotic therapy should be given intramuscularly every three hours until temperature is normal and all evidence of infection has disappeared As the patient improves therapy may be gradually discontinued until the patient is ready to be re established on some routine form of therapy

Acute Adrenocortical Insufficiency (Surgical)

Acute adrenocortical hypofunction may appear secondarily to surgical procedures on the adrenal gland or following trauma or operative procedures in patients with covert hypofunction In both these situations the precipitating cause is the associated traumatic stress and the inability of the cortex to respond When surgery is planned on one or both adrenal glands for tumor or hyperplasia of the medulla or cortex it is best to use prophylactic therapy preoperatively to prevent the development of adrenal crisis Since the adrenal cortices are functioning corticotropin (ACTH) may be used to stimulate them to produce a high concentration of circulating adrenocortical steroids prior to operation

Prophylactic Treatment Treatment should be begun forty-eight to seventy two hours before operation by intramuscular

* See also Chapter 19

uting to electrolyte imbalance) and require the diet to contain liberal quantities of potassium since hypopotassemia is a most dangerous complication

Desoxycorticosterone acetate is begun with injection of 2-3 mg daily The patient s body weight blood pressure and water intake and output should be followed closely during the initial phase of therapy as indices of retention of sodium with consequent overhydration Puffiness about the eyes in the morning or ankle edema at night are early signs of sodium retention The roentgenographic cardiac silhouette is another valuable guide to therapy, once a normal heart size has been attained, it is dangerous to increase desoxycorticosterone dosage further

In the absence of weight gain or elevated blood pressure the dose may be increased by 0 5 mg every forty-eight hours This must be done cautiously and if edema or weight gain of more than 0 5 kg occurs subsequently the drug should be discontinued and then begun at a lower level of dosage twenty four to forty-eight hours later when the signs have subsided The dose should rarely exceed 5 mg daily since 90 per cent of patients are controlled below this level It will be necessary to readjust dosage several times during the first few months (most frequently to smaller doses) because as circulation, hydration and gastrointestinal absorption improve all body metabolism is enhanced including that of the remaining functional adrenal tissue If *sodium chloride* is being used for supple*mentation* the patient must be followed more carefully since with improved adrenal function and decreased exogenous hormone requirement, the likelihood of sodium and *chloride retention* and excessive potassium excretion is increased If edema appears, the sodium chloride should be stopped and after forty eight or seventy two hours begun again at a 1 Gm per day lower level Appearance of muscle weakness during active treatment is usually a sign of a high sodium potassium ratio and requires administration of potassium citrate 0 8-1 6 Gm three or four times daily The dosage of desoxycorticosterone should be reduced materially and lipo adrenocortical extract 1 cc twice daily substituted for several weeks

Once the patient s average daily dosage need has been established and stabilized pellet implantation may be considered Pellets are supplied in two sizes (1) 125 mg, which release approximately 0 75 mg of desoxycorticosterone daily and (2) 75 mg which release approximately 0 50 mg The number of pellets used daily is computed by the daily hormone requirement i e, 3 0 mg—6 of the 75 mg or 4 of the 125 mg

It is safer to use slightly less of the hormone in the form of pellets than would seem required by daily injection and utilize sodium chloride supplementation of 3-6 Gm daily if needed to make up the difference The implanted pellets provide a constant supply of hormone and seem more efficient than daily injection If signs of overdosage appear after pellets have been introduced the sodium chloride should be discontinued, dietary sodium chloride reduced, and potassium citrate given in 20 per cent solution, 1 6-2 4 Gm two or three times daily in fruit juice

The usual site of pellet implantation is the infrascapular region After local anesthesia of the area the pellets are placed in muscle tissue in a stellate arrangement some distance from the line of incision The smaller sized pellets may be implanted by a special trocar Hemostasis is important because bleeding may float the pellets from their positions and extrusion may occur

The patient's blood pressure, body weight, general feeling tone and ability to carry on normal activities should be recorded As the pellets are gradually absorbed, inadequate exogenous hormone

tory therapy) may be used in the secondary type

Addison's Disease

This classical type of adrenal insufficiency was first described by Addison in 1855 It is a rare disease that occurs in adult life most often between the third and fifth decades Since tuberculosis of the adrenals is apparently the etiologic factor in approximately half the cases encountered, active tuberculous foci must be sought in every case of Addison's disease When tuberculosis is discovered it should be treated as outlined in the chapter on pulmonary infections * The most frequent cause of nontuberculous primary Addison's disease is a focal necrosis and atrophy of the cortex The etiology of this atrophy is not known although it has been suggested that vascular infarction or exhaustion following chronic stress may be responsible Rarely amyloidosis and cancer may cause adrenocortical destruction and Addison's disease

The diagnosis of Addison's disease should be entertained in any patient who complains of a symptom complex of weakness and fatigability, weight loss and changes in skin pigmentation If on examination hypotension is found the index of suspicion should rise The patient should be questioned thoroughly for a history of recurring gastrointestinal upsets anorexia nausea and vomiting The Thorn test for the level of circulating eosinophils is one of the most valuable diagnostic measures Essentially this test requires (1) a preliminary or control eosinophil count during the fasting state (2) intramuscular injection of 25 U S P units of corticotropin and (3) four hours later a second eosinophil count The patient may be given a meal immediately after the injection but should not be fed prior to the second count A fall of 50 per cent or more in circulating eosinophils excludes adrenocortical insufficiency To exclude adrenal insufficiency secondary to pituitary failure the Thorn test may be performed substituting 0 3 cc of 1 1000 epinephrine subcutaneously for the corticotropin Otherwise, the procedure and interpretations remain the same Thus if the corticotropin test shows satisfactory eosinophil response but the epinephrine test is followed by a poor response, pituitary involvement is indicated Various other more complicated procedures such as the Conn test for determination of the sodium and chloride concentration of sweat, or the Robinson Power, Kepler water test may be performed for further verification and information regarding the severity of the process For the performance of these and other diagnostic tests it is suggested that the reader consult Chapter 49

Treatment As emphasized previously the treatment of Addison's disease is complicated by the probable presence of active tuberculosis Patients with active tuberculosis have shown rapid progression of lesions when treated with cortisone It is imperative to treat the tuberculosis concomitantly probably with streptomycin and *p* aminosalicylic acid while treating the Addison's disease

The diet should be high in calories carbohydrate and protein supplemental feedings should be encouraged to maintain the patient's carbohydrate reserves while on desoxycorticosterone

In chronic adrenocortical insufficiency, *maintenance therapy* may be begun if the patient is not in crisis or has been stabilized following crisis Main reliance is still placed on desoxycorticosterone acetate with or without supplemental salt because of its availability relatively low cost, and the sum of experience with this form of therapy Sodium chloride 3-6 Gm daily, lowers the basic desoxycorticosterone acetate requirement Thorn and others have abandoned the use of supplemental sodium chloride as potentially dangerous (contrib-

* See Chapter 16

the circumstances a variety of syndromes of adrenal cortical origin may occur which differ in accordance with the predominant hormones present and with the age and sex of the patient at the onset The clinical picture of tumor of the adrenal cortex may be indistinguishable from bilateral hyperplasia or from secondary hyperplasia due to basophilic adenoma of the anterior pituitary gland Today it is generally agreed that Cushing s syndrome refers to primary adrenocortical hyperfunction while Cushing s disease refers to secondary adrenocortical hyperfunction (basophilic adenoma) Both conditions have similar signs and symptoms

Adrenocortical hyperfunction may be subdivided as follows

1 *Adrenogenital syndrome*
   a Pseudohermaphroditism
   b Prepuberal masculinization
   c Virilization
   d Feminization
2 Cushing s syndrome

Adrenogenital Syndrome

In adrenogenital syndrome the adrenal steroids are metabolized largely to androgenic degradation products or the cortex secretes androgenic corticoids in abnormal *quantities The response of the patient* varies markedly, dependent upon the age and sex at onset

Pseudohermaphroditism Pseudohermaphroditism reflects the virilizing effects upon the female fetus Enlargement of the clitoris small labia majora and minora and other anatomic defects of the genital system result

Prepuberal Masculinization Should hyperplasia of the adrenal cortex occur postnatally but in early childhood somatic and sexual precocity predominate In boys there occurs marked development of the external genitalia muscular and skeletal development of adult type and pubic hair growth The child may resemble an infant Hercules In girls a male pseudohermaphroditism develops with enlargement of the clitoris and pubic hair growth

Virilization If the onset of adrenocortical hyperplasia is delayed until after puberty virilization of the female occurs menses cease the breasts become smaller a *characteristic acne and baldness may* develop the voice deepens beard growth occurs and the musculature becomes more masculine In males this condition cannot be distinguished from the normal puberal changes

Feminization Feminization rarely occurs in the adult male and only in association with a malignant form of adrenocortical tumor It is characterized by atrophy of the testes and enlargement of the breasts

Treatment Although cortisone has been reported to cause virilization in females recent reports indicate that cortisone may be of value in the treatment of pseudohermaphroditism and prepuberal masculinization Further experience with the use of the hormone is necessary before the results may be evaluated Surgical ablation of adrenal tissue or tumor if present has occasionally reversed the course

Cushing s Syndrome and Cushing's Disease

Both *conditions present* essentially the same clinical picture of hypertension florid facies hirsutism trunk obesity abdominal striae and osteoporosis with amenorrhea in women and decreased libido in males Buffalo hump acne glycosuria *and muscle weakness are less constant* findings The diagnosis can be verified by examination of the urine for the 11 17 oxysteroid excretion levels which are invariably elevated while 17 ketosteroids may be only slightly increased or normal * *The blood findings reveal eosinopenia* lymphopenia and polycythemia a relative hypopotassemia and a tendency to alkalosis The glucose tolerance curve is flat

* See Chapter 49

supply gradually ensues This hormone lack is indicated by anorexia weight loss drop in blood pressure and fatigue Increase in sodium chloride supplementation aids temporarily but usually intramuscular injections of desoxycorticosterone acetate 0 5 1 0 mg daily are required with gradual increase in this dosage as less and less hormone is available from the pellets Usually the pellets are completely exhausted within nine to twelve months When the patient has been restabilized on daily desoxycorticosterone acetate injections usually at a lower dosage than required originally pellets again may be introduced

The great disadvantage of desoxycorticosterone therapy is its lack of protection against sudden stress situations due to disease surgery pregnancy injury or emotional upset Under these circumstances immediate supplementation with aqueous or lipo adrenocortical extracts or the 11 17 oxysteroids becomes imperative to avoid Addisonian crisis Furthermore an imbalance of carbohydrate protein and fat metabolism constantly exists despite the high calorie high carbohydrate and high protein diet The patient thus is balanced only for the immediate situation and possesses scant reserves for emergencies

It is apparent that cortisone or hydrocortisone with sodium chloride alone or with desoxycorticosterone supplementation are preferable in the treatment of Addison s disease since a more normal homeostasis can be attained than with desoxycorticosterone alone or with salt Furthermore cortisone and hydrocortisone may be taken orally and in the doses employed do not tend to induce the toxic side-effects of desoxycorticosterone While experience is limited it has been found that 25–75 mg of cortisone daily administered orally and supplemented by 6–9 Gm of enteric-coated sodium chloride tablets maintained normal fasting blood sugar levels normal electrolyte balance and caused fading of pigmentation weight gain and increased muscle strength in a small group of patients

Side effects of cortisone treatment in Addison s Disease Hypertension is the chief side effect seen although acne and hirsutism have also been reported. When tuberculosis is present cortisone should be used if at all at minimal dosage levels and with due caution against the possibility of acceleration of the tuberculous process

In Addison s disease secondary to anterior pituitary hypofunction there usually is a concomitant failure of the other major target glands the thyroid and gonads In these circumstances adrenal hypofunction is manifested by profound carbohydrate deficiency rather than electrolyte and pigmentary changes The thyroid and adrenal normally exist in a state of equilibrium increase in the function of one gland generally depresses the function of the other Therefore it is important to use substitution therapy for the pluriglandular deficiency rather than for one gland alone thus avoiding further depression of an untreated gland However since thyroid overdosage may precipitate adrenal crisis it should be given cautiously and increased very gradually

If *thyrotoxicosis* complicates Addison s disease thyroid function must be reduced quickly or the increased adrenal hormone requirement will bring on adrenal crisis Antithyroid therapy should be promptly employed as discussed in the section on the thyroid gland

ADRENOCORTICAL HYPERFUNCTION

Adrenocortical hyperfunction may be due to hyperplasia or neoplasia Overproduction of corticosteroids and their metabolites may be (1) predominantly of androgenic or estrogenic type (2) predominantly of metabolic control type or (3) various combinations of the two previous types Under

definite value in establishing the nature of the hypertensive manifestations *

Benzodioxane Test 2 (1 Piperidyl methyl) 1 4 benzodioxane an adrenolytic agent in 2 per cent solution is injected intravenously over two minutes in a dosage of 0 25 mg per kg body weight If a significant drop in both systolic and diastolic pressures occurs shortly after injection and is maintained for approximately fifteen minutes then pheochromocytoma is present If no fall in blood pressure occurs some other cause for the hypertension should be sought

"Dibenamine" Test Slow intravenous injection of 7 mg of dibenamine hydrochloride (N N dibenzyl β-chloroethylamine hydrochloride) per kg body weight produces a significant and more persistent fall in blood pressure than with benzodioxane

Histamine, Tetraethylammonium Bromide, and Methacholine Chloride Tests These tests incite or precipitate a characteristic paroxysmal attack in the patient They may be used for verification in the paroxysmal type but are not as reliable as the benzodioxane test and may produce dangerous hypertensive effects

Perirenal Insufflation Perirenal insufflation of oxygen followed by roentgenograms may reveal the existence of tumor in one or both adrenal glands.

* See also Chapter 48

Treatment of Pheochromocytoma

Once the diagnosis is established the only effective treatment is ablation of the responsible tumor tissue Control of the acute attack is symptomatic For the sustained type the intravenous infusion of dibenamine hydrochloride (see the test) 7 mg per kg body weight dissolved in 300 cc of 5 per cent glucose over a period of an hour may be followed by a remission of hypertension for twenty four to forty-eight hours As soon as the patient is reasonably well surgery should be performed Adequate supplies of epinephrine blood and other fluids should be available to combat sudden drops in blood pressure It is usually wise to prepare the patient as described for prophylactic treatment in adrenal surgery At operation a thorough search should be made for aberrent tumors as these occur in a significant number of cases During the surgical procedure wide fluctuations in blood pressure occur especially on manipulation of the tumor

Postoperatively the patient should be treated with adrenocortical substitution therapy as described previously under adrenal surgery

of the flat bones Perinephral insufflation of oxygen may demonstrate adrenal tumor or hyperplasia

Treatment of Cushing's Syndrome and Disease

Only temporary relief may be obtained by medical treatment *Testosterone propionate* in 25 mg doses daily promotes protein anabolism, tends to overcome osteoporosis, and reduces muscle weakness and glycosuria to some degree

Subtotal adrenalectomy is the treatment of choice for primary adrenocortical hyperfunction and removal of as much as 90 per cent of both adrenals has produced promising results The surgery must be radical, otherwise recurrence is most likely The patient should be managed pre and post operatively as indicated in the discussion on adrenocortical hypofunction due to adrenal surgery

Cushing s disease may be treated similarly to Cushing s syndrome including the surgical ablation of one and greater part of the other adrenal gland The reaction after surgery, however may be more difficult to control and pancreatic complications such as fat necrosis and cysts have been reported Irradiation of the pituitary has been followed by equivocal results The technical difficulties of delivering sufficient dosage to the pituitary and its high resistance probably are factors When improvement does take place after irradiation it is usually slow and undramatic

HYPERFUNCTION OF THE ADRENAL MEDULLA

The adrenal medulla may well be regarded as an extension of the autonomic nervous system It receives many preganglionic fibers derived from the spinal cord which run, apparently without synaptic interruption, to the medullary cells

Embryologically, it is derived from the neuroectoderm, and apparently from cell origins similar to the autonomic nervous system Sympathogonia cells migrate through the forming cortex to the medullary area The sympathogonia cells are the common origin for both the ganglion cells and the pheochromocytes of the medulla The latter secrete the medullary hormones

Hyperfunction of the adrenal medulla is almost always associated with rare adrenal medullary tumors of pheochromocyte origin (pheochromocytoma) Other tumors of the medulla do not cause hyperfunction and usually are of neurogenic type such as neuroblastoma and ganglioneuroma

Pheochromocytoma

This tumor of the adrenal medulla arises in the cells responsible for production of epinephrine and norepinephrine It has been reported at all ages, but is most frequently encountered in young adults Some patients may have no complaint but note a palpable enlarging abdominal tumor Most patients complain of the effects of excess of epinephrine and norepinephrine secretion, i e sudden attacks of palpitation accompanied by anxiety tremors, headache, dizziness, precordial compression and pain epigastric distress, nausea, and vomiting The skin in an acute attack is cold and clammy with circumoral pallor The extremities are cold with subjective symptoms of numbness and tingling Vision is impaired the pupils dilated The pulse rate is very rapid The blood pressure fluctuates paroxysmally ranging from 100–150 mm Hg to 250–300 mm Hg systolic with corresponding but relatively lower diastolic pressures A third smaller group of patients exhibits a symptom complex more closely allied to that of essential hypertension than the asymptomatic or paroxysmal types just described Certain diagnostic tests are of

spain may not be entirely avoided The insurance statistics of Dublin reveal however that each decade since the advent of insulin has led to a longer life expectancy for the diabetic patient This is because of increasingly better by the physician and cooperat patient

Physiology

IF GLUCOSE is not used because of lack of insulin a chain of events occurs First a rise in blood sugar takes place above the normal limits of 80–120 mg per 100 cc due to inability of renal tubular phosphorylation to keep pace with the excess of sugar In diabetes of long standing however adaptation apparently takes place and glycosuria may not appear with blood levels up to 0 25–0 3 Gm per 100 cc The sugar available for excretion is first derived from ingested glucose This normally would be oxidized converted to liver and muscle glycogen or used in the synthesis of amino acids and fatty acids

Failure of utilization soon results in glycolysis of liver glycogen By an unknown mechanism a falling liver glycogen results in increased mobilization of fats as fatty acids to be brought to the liver Similarly failure of amino acid (and thus protein) synthesis prevents correction of the breakdown of tissue proteins required to provide amino acids to the liver for gluconeogenesis

The excessive mobilization of fat has two consequences The normal end products of fat metabolism in the liver are acet and acetoacetic acid These normally the blood and are burned primarily muscles at a rate equal to that of formation In the presence of diabete formation of these products is in exce that which can be handled Interconver of acetic acid excess then occurs in the l to form ketone acids and acetone

The unchecked breakdown of tissue pr teins results in excessive deamination wi the loss of nitrogen to the body as ure nitrogen and of the glucose thus formed as glycosuria Glucose excretion carries with it body water A negative potassium bal ance follows the breakdown of proteins and the loss of intracellular water as de hydration progresses This potassium loss appears early

The underutilization theory currently does not imply as formerly that glucose utilization stops completely The brain and other tissues have an inherent though limited capacity to use sugar independently of insulin

Insulin

INSULIN is secreted from the beta cells of he islets of Langerhans in the pancreas It s an incomplete protein lacking in meth onine rich in cystine and depending on e disulfide bonds of cystine for its activity Its molecular weight is about 35 000

The immediate consequence of insulin lack is hyperglycemia while an excess causes hypoglycemia The mechanisms of action of the hormone are largely un

31. Diabetes Mellitus

JOHN A. LUETSCHER, JR.
& SIDNEY C. WERNER

Etiology

UNDERUTILIZATION of glucose is thought by most investigators to be the operative mechanism in idiopathic diabetes mellitus An absolute lack of insulin is thought to exist due to failure of secretory capacity of the beta cells of the islets of Langerhans However this point of view has been challenged by Soskin and others who favor the hypothesis that there exists only a relative insulin lack and that the prevailing mechanism in diabetes is over production of glucose from adrenal and pituitary overactivity Again overproduc tion could be interpreted either as excess gluconeogenesis or as inhibition of glucose oxidation with piling up of unused sugar as a result of the pituitary or adrenal hor monal effects

Stetten has examined both hypotheses experimentally in the rat He produced insulin lack by injury to the beta cells of the pancreas with alloxan and renal diabetes with losses of sugar via the urine with phlorizin No greater loss of sugar resulted from lack of insulin than occurred with renal glycosuria This suggests that overproduction does not follow insulin deprivation However this work does not rule out the possibility that pre-existing overproduction may be a cause of even tual failure of the pancreas in human diabetics Such a possibility is suggested by the fact that total pancreatectomy in non diabetics results in a diabetes of only mild severity since an average of 50 units of insulin restores carbohydrate metabolism to normal after operation whereas many spontaneous diabetics especially when in fection exists may require far larger amounts of insulin However, the higher insulin requirements of spontaneous dia betes are also taken into account by the underutilization theory in view of the possibilities of either increased tissue needs for insulin or of insulin inactivation in the severe diabetic Definitive studies are still needed

The mechanisms responsible for the pro duction and continuance of diabetes mel litus remain obscure Insulin appears to provide specific replacement therapy Nevertheless long term follow up studies tend to reveal that the replacement as at present given may be incomplete since vascular complications and a shortened life

absorption of glucose with phlorizin served this purpose It is interesting that these maneuvers are ineffective in the dog once hyperglycemia has been established The same is probably true of the human

Permanent damage to the beta cells of the pancreas in the experimental animal also can be produced by the pyrimidine alloxan diabetes mellitus follows Attempts have been made in man to deliberately injure these cells in spontaneous hypoglycemia with and without adenoma and with adenocarcinoma of the pancreas, but these efforts so far have been fruitless

UTILIZATION OF INSULIN

Insulin opposes other endocrine forces which tend to mobilize sugar or decrease its utilization The administration of insulin to the diabetic patient reduces blood sugar but causes a rise in liver glycogen content and to a lesser extent in muscle glycogen There is also a shift in respiratory quotient to that seen when carbohydrate is being burned In the normal animal muscle glycogen formation may predominate after insulin administration to such an extent that the blood sugar is decreased and liver glycolysis induced Thus there is a lowering of liver glycogen rather than the increase seen following insulin in the diabetic Cardiac muscle glycogen decreases following the injection of insulin This is important in the regulation of older diabetics with impaired heart muscle where insulin shock must be avoided for this reason

Liver glycogen formation accounts for only 3 per cent of the total glucose metabolized in twenty four hours by the rat This has been established by the isotopic studies of Stetten and his collaborators Glycogen is formed from glucose Glucose is available (1) from the ingestion of glucose (2) from gluconeogenesis consequent to the breakdown of certain amino acids and fats (glycerol fraction) derived from the body s own stores (3) from synthesis in the liver and (4) from lactic and pyruvic acids produced mainly in the muscles A complex chain of enzymatic reactions involving the phosphorylation of glucose is required to elaborate muscle and liver glycogen A specific phosphatase in turn is required to release glucose from glycogen This enzyme is present in the liver but not in muscle so that muscle glycogen metabolism cannot result in the liberation of glucose

The limited amount of liver glycogen available to the body indicates that this substance serves primarily to maintain a more or less constant blood sugar level and provide an emergency source of glucose Epinephrine is responsible for such liberation of glucose by promoting the breakdown of liver glycogen When liver glycogen stores are low, epinephrine appears to decrease muscle glycogen with the liberation of lactic acid for conversion in the liver to glucose or glycogen

Gluconeogenesis the synthesis of glucose results largely from the action of enzyme systems within the liver concerned with the handling of three carbon fragments These fragments result from the breakdown of protein and carbohydrate and include (1) the glycerol released from the splitting of fat (2) certain amino acids from protein and (3) the lactate and pyruvate elaborated by the muscles

Ingested carbohydrate reaches the liver only as a hexose since it is split into glucose fructose, and galactose in the gut. It is thought to be phosphorylated in the gut wall during passage into the portal circulation Stetten estimates that in the rat about 70 per cent of the glucose is resplit to three carbon fragments and is either oxidized in the muscles—mainly by means of the tricarboxylic acid cycle—to carbon dioxide and water or is shifted to amino acid synthesis and consequently to protein formation The remaining 30 per cent of metabolized glucose is converted to fatty acids

known The main metabolic disorder for which insulin is used therapeutically is diabetes mellitus Here, too the pathologic mechanisms which result in the disorder are obscure In general, insulin opposes those other endocrine secretions which serve to mobilize glucose or decrease its utilization The metabolism of carbohydrate, fat, and protein are highly interrelated Thus, derangement in the metabolic pathway of one ultimately causes serious interference with the metabolism of the others

SECRETION OF INSULIN

The secretion of insulin is thought to be under endocrine nervous and chemical control Young has shown that certain anterior pituitary extracts increase the size and insulin content of the islets of Langerhans in the dog the so-called insulinotropic effect Mirsky has found that chronic injections of insulin lead in time to atrophy of the beta cells of the islets Also transient diabetes is known to follow the removal of an insulin secreting pancreatic adenoma which had caused hypoglycemia These observations suggest that there may be a possible reciprocal relationship between the insulinotropic function of the anterior pituitary and insulin secretion According to this hypothesis excess insulin suppresses the output of the pituitary principle controlling beta cell activity which causes decreased secretion of insulin whereas lack of insulin promotes the converse This system of balance has been demonstrated between the anterior pituitary and most of its related glands such as the thyroid

The vagus nerve stimulates secretion of insulin Increased vagal activity is held by some to be responsible for the tendency to hypoglycemia and the flat glucose tolerance curve found in certain psychoneurotic states The studies bearing on this point suffer from lack of standardization of diet prior to the testing of glucose tolerance Control over the preceding diet is of utmost importance in assessing glucose tolerance A high carbohydrate diet will generally cause a flat glucose tolerance curve, whereas a fat rich diet usually results in a diabetic type of curve Young has shown that this effect is mediated through the anterior pituitary

Variation in the blood sugar provides a chemical stimulus to insulin secretion Hyperglycemia causes the beta cells to secrete Hypoglycemia however, activates the adrenal medulla which releases epinephrine and causes glycolysis in the liver Prolonged hyperglycemia produced by sugar fed to the partially depancreatectomized dog or by the injection of diabetogenic extracts of the anterior pituitary in the intact dog and cat may result in permanent diabetes mellitus This presumably is due to ultimate exhaustion of the beta cells secondary to the attempt to provide excesses of insulin in response to the elevation of blood sugar Hydropic degeneration of the beta cells is ultimately found similar to that frequently seen in human diabetes

Best Haist, and Campbell have shown that the diabetes thus provoked can be completely prevented by the concurrent injection of insulin or by the administration of low carbohydrate diets This suggests that increased food intake is the most severe constant stress which may precipitate diabetes in the potential diabetic It is evident also from the work of Lukens and Dohan in the partially pancreatectomized cat that diabetogenic pituitary extracts do not produce direct injury to the beta cells Thus these investigators observed that the diabetes usually resulting from anterior pituitary extract administration could be prevented in the interval following the establishment of hyperglycemia and before the onset of fibrosis of the islets by restoring normal levels of blood sugar A low carbohydrate diet, the administration of insulin or the prevention of tubular re-

bulk of energy comes from its high fat content, which may be unacceptable to the patient or undesirable in its tendency to produce high blood lipids or to favor the formation of ketone acids or (3) the use of insulin to allow the utilization of a more nearly normal amount of carbohydrate Diets inadequate in calories should be reserved for the overweight patient whose tolerance for carbohydrate usually improves with weight reduction The combination of insulin and a very low carbohydrate diet is a therapeutic absurdity leading to either hypoglycemia or ketosis and often to both at once urgently demanding an increased carbohydrate ration Insulin should be used primarily to allow increased utilization of sugar not to lower the blood sugar

The maintenance of an approximately normal blood sugar is desirable in the mild diabetic Sluggishness polyuria and pruritis disappear Diabetes itself will often regress under accurate dietary control but under poor regulation the tolerance for carbohydrate sinks lower Insulin requirement is often reduced under accurate regulation and the blood sugar may be more stable provided that adequate carbohydrate is given with the insulin

Many severe or labile diabetics however pay too high a price for the attempt to keep the blood sugar normal Hypoglycemic reactions are distressing and dangerous for any patient but for patients who must drive a car or perform some hazardous job or whose coronary circulation is impaired the risk of a reaction is intolerable Such patients must not be regulated so closely that reactions are likely to occur The penalties of moderate hyperglycemia in the severe diabetic receiving adequate insulin and carbohydrate are ill defined and remote while a hypoglycemic reaction presents an immediate and very real danger Only an absolute faith in a physician's statement that glycosuria is more dangerous … reaction will make a patient continue on too strict a course The physician must not make such a statement lightly on the basis of the present inadequate evidence

The appearance of ketone acids in the urine is now generally thought to reflect an increased rate of partial combustion of fats caused by a severe reduction in the storage and utilization of glucose Ketonuria in diabetes is usually accompanied by heavy glycosuria and calls for immediate insulin treatment In the rare case when glycosuria is minimal or absent, ketonuria is best treated with large amounts of carbohydrate with only enough insulin to prevent hyperglycemia

GENERAL PROBLEMS OF TREATMENT

The treatment of diabetes presents ce
tain peculiar problems

1 The disease is going to last a lifetim
The patient can look forward to so
symptomatic improvement rarely to a
mission almost never to freedom from
of relapse if treatment is neglected
diagnosis must therefore not be
lightly In doubtful cases strict dieta
striction should not be instituted
diagnostic tests are completed so as
confuse the interpretation Other ca
glycosuria and hyperglycemia m
ruled out

2 Strict dietary regulation is
invade the patient's personal life
turbing degree He can never
down to a good dinner and eat
happily filled His meals becom
sacrifice of appetite to the go
blood and urine sugar Dining o
a calculated risk travel is a ha
holiday an upsetting experienc
tients accept this in a matter o
way and settle down quickly
learn Others never recover f
and spend the rest of their liv
evasion or frank lack of coo

In the utilization of glucose, phosphorylation is the first step This is mediated by the enzyme, hexokinase to form glucose 6 phosphate The Coris have shown that hexokinase is inhibited both in vitro and in vivo by a fraction in pituitary extracts which interferes with the first step in the cycle of degradation of glucose Insulin opposes this inhibition and increases the normal anaerobic breakdown of glucose to three carbon fragments which ultimately are aerobically burned to carbon dioxide and water or are converted into fatty acids As a direct or indirect effect of increased glucose oxidation the synthesis of certain amino acids used in building body protein is promoted The increase in glucose utilization which follows insulin in the diabetic restores to normal the metabolism of fat and protein Nitrogen is thus spared or stored and the excess of ketone bodies is abolished

Inability to burn sugar therefore may result from two causes First there may be an absolute lack of insulin with under utilization of available glucose Second, there may be a relative lack of insulin due to an excess of other hormones especially those of the anterior pituitary and adrenal cortex This leads to overproduction of glucose consequent to excessive gluconeogenesis or as an alternate possibility, the piling up of sugar because of the inhibition of normal glucose oxidation e g, hexokinase inhibition Such 'overproduction' is seen in acromegaly where there is probably excessive anterior pituitary activity

The relations of the anterior pituitary to the adrenal cortex are of interest in this connection The anterior pituitary appears to exert its effects almost entirely through the mediation of the adrenal cortex Thus certain adrenal cortical steroids given to the hypophysectomized animal correct almost all of the disturbances in carbohydrate metabolism consequent to the loss of the pituitary, except for the maintenance of muscle glycogen Similarly, adrenalectomy in the diabetic cat reproduces the Houssay experiment of alleviation of diabetes by hypophysectomy The adrenal steroids involved have an oxygen at the eleven carbon position, namely, corticosterone, 11-dehydrocorticosterone etc

Thus overproduction,' in the sense

activity but here there is a rapid breakdown of liver glycogen initiated by the epinephrin The action of epinephrin is the same whether injected, secreted during stress or excessively released in pheochromocytoma of the adrenal medulla

General Aims and Approach to Therapy

THE chief aim of treatment in diabetes as in any other disease is a patient restored to health and vigor able to do his work and to enjoy life with a minimum of inconvenience from his disease or from therapy

To approach this happy state in the treatment of diabetes the physician has two major weapons diet and insulin The purpose of the diet is to supply enough energy and accessory factors to keep the patient in a state of proper nutrition and vigor without exceeding his ability to use carbohydrate If the carbohydrate tolerance is low compared with energy demands several alternatives present themselves (1) a diet inadequate in calories, which is a temporary measure (2) a diet in which the

ance at the moment, to be interpreted in the *light of the general clinical picture* They aid in approximating the necessary *dietary restrictions*

HISTORY

A complete history is essential, with special reference to previous diet habits, weight, symptoms of diabetes and complications *and results* of treatment, if any The cook or the family budget may change the whole plan of treatment A clear picture of the patient's daily activity and employment is important Finally, the patient's and his family's reaction to the illness must be assessed, and any incipient rebellion averted by directing the patient's energies into more useful channels of learning and cooperation

EVALUATION OF THE PATIENT'S DIABETIC STATUS

The *patient should* be placed temporarily in one of the following general *classes as suggested by Loeb*

hydrate content, and a limited ration of fat (See columns 1 and 2, Table 29) Planned exercise may be helpful

Further plans are based, as always on results If weight loss goes on at the expected rate (0 2–0 8 kg per week), the diabetes may quickly disappear As body weight approaches the ideal, the diet can be expanded until weight loss stops At this *point, some* patients may be able to take an essentially normal diet, refraining only from using sugar and sweets and keeping *the weight constant Others may* have to limit carbohydrate intake more carefully to avoid a recurrence of hyperglycemia and glycosuria Follow up should be regular and frequent through this test period but *subsequently the patient* can be *thrown* largely on his own He must weigh himself and test his urine once a week He should be seen by the physician at routine intervals of three to six months, and should report at once if any problem arises in the *interval*

	A	*B*	*C*
Weight	Above average	About average	Average or below
Rapid loss of weight	Absent	Absent	Present
Polyuria	Slight or absent	Slight or absent	Present
Usual age at onset	*Over 50*	*Over 40*	Below 40

Group A will usually respond to a moderately restricted diet without insulin Group B may require severe carbohydrate restriction or insulin Group C will usually require insulin for proper regulation Infection or other serious complication usually makes the use of insulin advisable in any of these groups while ketonuria with glycosuria demands the immediate use of insulin in any diabetic patient

Group A

The patient is placed on a 1200–1500 calorie diet containing a normal ration of protein no foods made with sugar, very limited amounts of foods of high carbo

If the weight does not decrease, it is evident that the patient is not following *the diet If the diabetes is of moderate* severity, there may be a temptation to administer insulin which is *highly undesirable*, since it makes future weight reduction very difficult It is much more *satisfactory* to try to arrange a situation in which the patient finds it difficult to *cheat Such* patients usually refuse hospitalization The effort required to *handle them as out* patients is rarely justified by the results

Group B

This patient has little or no *weight to* spare, while his diabetes is less easily con

3 Under the single heading of diabetes, we include a variety of clinical pictures whose extremes have little in common

a The mild obese elderly diabetic who needs only a moderate restriction of calories and carbohydrate to control hyperglycemia

b The case on the borderline of insulin need who can get along without insulin only on the most strigent restriction of carbohydrate and who may need insulin later to avoid malnutrition or to cope with increasing severity of the diabetes

c The moderately severe diabetic who must take insulin to avoid heavy glycosuria weight loss symptoms and ultimately acidosis

d The severe labile diabetic who must take large doses of insulin to escape the immediate threat of ketosis and acidosis but whose requirements vary from day to day so much that accurate regulation of the blood sugar is impractical

e The juvenile diabetic with special needs of growth high basal energy requirement great activity an immature outlook and too often a cruel environment of resentful parents and teasing friends

4 There is no known method of predicting insulin dosage and calculations of diet are only approximate Each step must be made empirically An orderly approach must therefore be planned We should start with a rough consideration of insulin requirements Does the patient need insulin immediately to keep him out of trouble? Attention can then be turned to the diet which should be adapted to the patient s basal needs activity and deviations from normal weight Finally the type and dosage of insulin is adjusted for the smoothest possible control of the blood sugar if this control can not be gained with a satisfactory diet

Order of Procedure for a New Patient

ESTABLISHMENT OF THE DIAGNOSIS IN THE MILD OR ASYMPTOMATIC CASE

Glycosuria accompanied by hyperglycemia is usually due to diabetes mellitus but excitement fever drugs hyperthyroidism and other rarer causes must be ruled out The minimal criterion is a fasting blood sugar consistently above 120 mg per 100 cc or hyperglycemia above 160 mg per 100 cc sustained for more than one hour after a meal containing about 100 Gm carbohydrate (such as 3 slices of bread 3 ounces of potato and a sweet dessert) If more carefully defined conditions are necessary for the borderline case a glucose tolerance test may be made by following the blood sugar and by testing the urine for sugar each hour for three or four hours after the ingestion of 1 5 Gm glucose per Kg body weight (100 Gm for a patient weighing 150 lb)

These tests require that the patient s preceding diet contain a liberal amount of carbohydrate To avoid the influence of previous diet on the results the dose of sugar may be divided in two equal parts and the two doses are given thirty minutes apart the blood sugar is determined while fasting just before the second dose and thirty minutes after the second dose If the blood sugar rises significantly (25 mg per 100 cc) after the second dose or if the blood sugar exceeds 160 mg per 100 cc the presumption is that the patient has diabetes Such tests must not be regarded as infallible proof of diabetes but are a useful measure of the carbohydrate toler

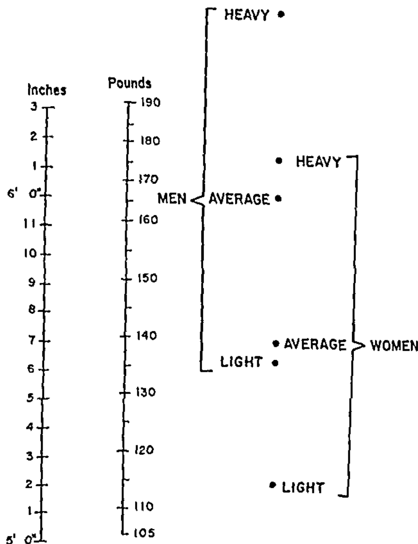


Fig 11 Relation between height, body frame, and ideal weight Given the height and the type of body frame judged from the bony structure as *heavy, average* or *light* a ruler or paper straight edge is placed between the height in inches and the point on the right hand side representing the appropriate sex and frame The point at which the straight edge crosses the pound scale gives the ideal weight It can be easily seen that only an approximation can be obtained because of the considerable variation with body frame

dinner Some patients will continue to do so unless the importance of spreading the load more evenly is specifically pointed out

Occupational factors must be noted A patient working on the night shift or on different shifts on different weeks is usually hard to regulate Many working people must carry lunch to work or eat the menu available in the cafeteria Patients who must travel or for other reasons must eat at restaurants are similarly handicapped The diet prescribed should take these factors into account Unusually long intervals between meals, especially at work, predispose

trolled than that of Group A His tolerance for carbohydrate is low, and he may have to take a very low carbohydrate high fat diet to avoid insulin injections on the one hand and progressive malnutrition on the other Most physicians find it easier for all concerned to use a maintenance diet of a more normal composition from the beginning using a small dose of insulin if the patient fails to respond promptly to diet alone The use of insulin offers good nutrition prompt control and greater stability of regulation during intercurrent infection or other disturbances The reluctance of some patients to start using insulin is natural but should not be given much weight in the decision Often with prompt and accurate control the insulin requirement declines and the patient may even be able to get along without insulin on an adequate and palatable diet

Group C

This patient is younger more active below ideal weight and has a more severe type of diabetes *He is going to require* insulin No useful purpose is served by putting this patient on a submaintenance diet On an adequate and well balanced diet he feels better, is stronger, and cooperates better while the physician finds him less subject to hypoglycemia or ketosis The blood sugar is generally most easily controlled when the diet contains 150–200 Gm carbohydrate The disadvantages of lower levels of carbohydrate intake have already been discussed At higher levels, the only immediate disadvantage may be transient glycosuria with more or less polyuria until regulation is finally adjusted

Stability of Diet

In all of these groups it is important to maintain a constant diet from day to day, so that after an initial period of trial, the diet and insulin can be adjusted to smooth out any irregularities of control This presents a chore in instruction for the physician and a chore in calculation and preparation of food for the patient There is at present no satisfactory way to avoid these duties upon which the success of regulation depends A part can be entrusted to the dietician but *much of the* detail must remain under the direct scrutiny and supervision of the physician

Diet

GENERAL FEATURES

The only total prohibition in the diabetic diet is against pure sugar and foods with sweetening or syrup Canned vegetables and fruit must be checked for added sugar All bottled drinks are forbidden The physician himself must guard against the prescription of elixirs cough syrups and other preparations containing sugar

No single diet will serve for every diabetic Personal and national food habits are hard to change Major changes lead to personal and social stresses dissatisfaction and frequent lapses of diet A good diet history is important, and this should be reviewed with the patient, and excesses or inadequacies pointed out As little as possible should be changed by edict, as much as possible by informing and rousing the patient s interest because the patient and not the doctor is going to determine the diet in the long run The physician can only observe and advise the patient actually does the job and reaps the reward or penalty

Timing and distribution of meals are as important as content Many people eat no breakfast little lunch and a large

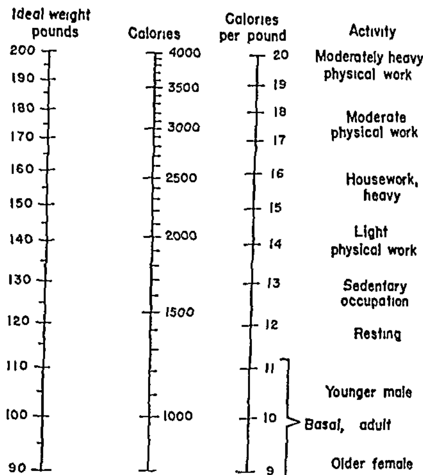


Fig 12 Relation between ideal weight activity and caloric needs Given the ideal weight and the degree of activity measured in calories per pound a ruler or paper straight-edge is placed between the known figures on the outer scales The caloric requirement is then read off the central scale at the point where the straight edge crosses the scale

hyperthyroidism demand further increases *These facts are generally accepted and* taught but their applicability to the diabetic is sometimes overlooked especially when the resultant energy demands make a conventional diabetic diet impossibly low in calories In the ensuing period of semi starvation the patient learns to eat a more adequate diet than the doctor has ordered, balancing the pressing demands of his body against the remonstrances of the physician When this has happened it is very difficult to regain the full confidence and cooperation of the patient

For these reasons, it is important to make all first diets tentative and to say *to the patient Follow this diet accurately for a* week or so and let us see what will happen to your weight and blood sugar If it is too little you will lose too much weight and then we will revise it In this way the patient becomes a partner in the regulation and knows that he has a voice in its revision

For the calculation of this first diet a good guess based on experience is often more accurate than calculations based on inadequate data As a starting point one may consult Fig 12 to obtain the caloric needs

to hypoglycemia if the patient is taking insulin Some severe diabetics must alter diet or insulin to compensate for unusual exertion or a day away from work Hazardous occupations and the driving of motor vehicles are doubly dangerous for patients taking insulin and between meal nourishment must be arranged to insure against reactions Some patients tend to overestimate their own strength of character for example a juvenile diabetic working as a clerk in a candy store

Religious and social factors must be anticipated Certain devout persons insist on observing fasts and feasts even though a liberal religious adviser has released them from the formal penalties of nonobservance Suitable arrangements should be made in advance of such major changes of routine if the diabetes is of any gravity Other patients crave sweets with all the intensity of the addict and a social supper at church or club is as upsetting as the visit of an alcoholic to a barroom Uninformed friends with hearty appetites and maudlin sympathy make dietary restrictions even harder For these reasons the patient should eat regularly at home prepare his own food when away from home and avoid social engagements involving food until his skill at dietary selection has been sharpened and his will power has been hardened

CALCULATION OF FIRST DIET

Although the physician will find many types of diet advised the most generally acceptable is one which approximates an average American diet with only the necessary restriction of carbohydrate Obesity may demand some restriction of fat In other respects, the diet should conform in types of food with what the average family would eat at any given meal thus minimizing the effort of preparing a diet and reducing the patient s feeling of being 'different

In prescribing the first diet for a new patient three factors enter the calculation (1) The patient s daily energy requirements, (2) The patient s excess or deficient weight, and (3) Special circumstances that may require a diet of minimum carbohydrate content

Calories for Maintenance at Ideal Weight

The energy requirements are difficult to predict accurately but a start can be made by determining ideal weight from the height and body build of the individual The ideal weight is found on the nomogram (Fig 11) or by the approximation shown in Table 29

TABLE 29 OPTIMAL WEIGHT FOR LONGEVITY

The average male of 5 8 should weigh 150 lb *
- Add or subtract 4 lb for each inch of difference in height
- Add or subtract up to 10 lb for variation of bony frame from average

The average female of 5 6 , should weigh 135 lb *
- Add or subtract 3 lb for each inch of difference in height
- Add or subtract up to 10 lb for variation of bony frame from average

Examples A man of 5 10 (2 above 5 8 ') of heavy bony frame should weigh 150+8 (2 ×4 lb per in) +10=168 lb

A woman of 5' 2 (4 below 5 6) of l ght frame should weigh 135−12 (4 ×3 lb per in)−10=113 lb

Calculated from maximum longevity tables of the Metropolitan Statistical Bureau See also Tab e 15
* We ght with average clothes and shoes but no coat.

Basal metabolic requirements are about 10 calories per lb body weight in most patients with diabetes (higher in younger males about 50 per cent higher in young children lower in older women) To this figure must be added the amount of energy consumed in the ordinary activities of daily life as judged from the history These will increase the energy requirements by 20 to 100 per cent above the basal level, and even higher in unusual circumstances Exposure to cold climate pregnancy, fever, and

TABLE 30 REPRESENTATIVE DIETS

Calories	1200	1500	1800	2100	2400
Breakfast					
Fruit (servings)	2	1	1	2	2
Cereal (servings)		1	1	1	1
Milk (cup)	½	½	½	1	1
Butter (teaspoons)	1	1	2	2	2
Crisp bacon (strips)				2	2
Eggs	1	1	1	1	1
Bread whole wheat or rye (slice)	1	1	1½	1	2
Cream (ounce)			1	1	1
Lunch				AVERAGE	AVERAGE
Meat very lean (ounces)	3	3	2	3	3
Group 1 vegetables (cups)	2	2	2	2	2
Butter (teaspoons)	1	2	2	3	3
Fruit (servings)	1	1	1	1½	2
Milk (cup)	½	1	1	1	1
Bread (slice)	½	1	2	2	3
Cream (ounces)					1
Dinner					
Meat (ounces)	3	3	3	3	3
Group 1 vegetables (cups)	2	2	2	2	2
Butter (teaspoons)	2	2	2	3	3
Fruit (servings)	1	1	1	1½	2
Milk (cups)	½	1	1	1	1
Bread (slices)	½	1	2	2	3
Cream (ounces)			1		1
Composition					
Protein (Gm)	80	90	90	100	[illegible]
Fat (Gm)	45	60	80	100	[illegible]
Carbohydrate (Gm)	120	145	180	200	

Prepared by Esther L Sippel Dietician Stanford University Hospitals

TABLE 31 TYPICAL BED TIME SNACKS FOR PATIENTS RECEIVING PROTAMINE ZINC INSULIN

Total dietary carbohydrate (Gm)		
Below 150	150 to 200	250 and over
1 cup milk 3 saltines	1 cup milk 1 slice bread ½ tablespoon butter	1 cup milk 1½ slices bread ½ tablespoon but[ter] ⅓ ounce cheese
Carbohydrate 20 Gm Calories* 200	Carbohydrate 28 Gm Calories* 300	Carbohydrate 4[illegible] Calories*

* Approximate figures

Obese Diabetics

As has been previously emphasized, in many obese diabetics simple weight reduction results in a great improvement or apparent disappearance of diabetes

The obese diabetic should be … porarily on a diet well below … lated from his ideal body wei… accelerate the weight loss P… should be held at a normal…

DISTRIBUTION OF DIET INTO CARBOHYDRATE, FAT, AND PROTEIN

In the diabetic diet, protein is given in normal amounts, carbohydrate is limited to meet the individual problem, and fat must make up the rest of the calories. Carbohydrate and protein yield 4 calories per Gm., while fat gives 9 calories per Gm.

Protein

A basic protein ration of 0.5 Gm. of protein per lb. ideal weight (i.e., 75 Gm. for a patient who should weigh 150 lb.) is prescribed in all cases. This is not reduced when weight reduction is in order, since a high intake is required to keep a patient in protein balance on a diet inadequate in calories. The protein ration may be increased to add calories or to cover the increased demands of growth, pregnancy, heavy muscular work, fever, or other complications. As the protein intake is raised above 100–120 Gm. per day, some resistance may be met because of cost or distaste. Since about one half of protein is converted into carbohydrate for metabolism, excessive protein intake may add a significant load of extra sugar.

Carbohydrate

No fixed limits should be set on carbohydrate intake, but patients should rarely be asked to subsist on less than 1 Gm. of carbohydrate per lb. ideal weight (i.e., 150 Gm. for a patient who should weigh 150 lb.) and few patients will require more than 1.6 Gm. (250 Gm. for 150 lb.). If the patient is being treated with diet alone, carbohydrate intake should be carefully adjusted to optimum tolerance, that is to the maximum intake which is compatible with an approximately normal blood sugar. An intake either much lower or higher in carbohydrate will impair his tolerance. If the patient is receiving insulin, the emphasis should be on finding the level at which the patient receives a satisfactory diet, but not to the extent that his diabetes becomes too difficult to control.

Fat

Fat fills out the gap in calories between carbohydrate plus protein and the body's demands. If both carbohydrate and fat intakes are limited, the body will burn its own fat. In the obese patient, this use of body fat is precisely what is desired, and the intake can be held at a very low level. In the underweight patient, on the other hand, no restriction need be placed on fat intake. It is rarely possible to get the fat intake above 0.8 Gm. per lb. ideal body weight (120 Gm. for 150 lb.) because of distaste or cost. The use of very high fat diets may allow a patient to escape the use of insulin by reducing the carbohydrate requirement to the bare minimum necessary to avoid ketosis, but this is an unstable balance bought with an unpalatable diet. It should be reserved for very special circumstances.

COMPOSITION OF FIRST DIET

A first diet of palatable composition may be made by using Joslin's formula, $C_2 F_1 P_{0.9}$, taking C as 1/10 of the desired number of calories. For example, to get approximately 2000 calories give carbohydrate 200 Gm. (800 calories), fat 100 Gm. (900 calories) and protein 90 Gm. (360 calories). This formula serves well in the most useful range of 1500–2600 calories. Below 1500 calories, further cuts should be made chiefly in fat, cautiously in carbohydrate, never in protein. Above 2600 calories the physician is apparently in uncharted waters, since most authorities condemn diets containing more than 250 Gm. of carbohydrate, while protein and fat are up to usual limits of tolerance. The physician must solve this problem either by reducing the requirements (easier work) or by increasing food that the patient will eat; otherwise the patient will take matters into his own hands.

TABLE 33 DIET SUBSTITUTIONS

1 slice of bread equals any one of these	3 large soda crackers 6 saltines 1/2 cup of any cooked cereal
1 ounce of lean meat equals any one of these	1 ounce of fish or 1 egg 3/4 ounce cheese 6 oysters, clams, or shrimp 1 rounded tablespoon cottage cheese, crab meat or drained salmon 3 small sardines, 2 1/2 inches long
1 serving of fruit equals any one of these	1 serving cereal 2 cups group 1 vegetable 1 cup group 2 vegetable 2 soda crackers or 4 square saltines

1 cup group 1 vegetable equal 1/2 cup group 2 vegetable
1 cup fresh milk equals 1/2 cup evaporated milk
1 tablespoon butter equals 1 tablespoon bacon fat oil, mayonnaise lard or margarine

FOOD WHICH MAY BE SUBSTITUTED FOR 1 SLICE OF BREAD IN DIETS WHOSE CHO IS 150 GM OR MORE

Artichoke, 1 medium sized	
Cereals	
All Bran	1/3 cup
Bran flakes	3/4 cup
Cooked cereal	1/2 cup
Cornflakes	3/4 cup
Corn canned fresh or frozen	1/3 cup
Corn on the cob fresh or frozen	1/2 medium sized ear
Lima beans fresh or frozen	1/2 cup
Macaroni (cooked)	1/2 cup
Matzoth	1/2 square
Peas fresh or frozen	1/2 cup
Potatoes Irish	(1/3 cup mashed 1/2 cup diced)
Oyster crackers	1/2 cup
Rice cooked	1/3 cup
Spaghetti, cooked	1/3 cup
Pep	3/4 cup
Rice Krispies	1/2 cup
Shredded Wheat	3/4 biscuit
Wheaties	1/2 cup

Adapted from outline prepared by Eloise R Trescher Nutrition Consultant for use in the Diabetic Clinic of the Johns Hopkins Hospital

DIVISION OF DIET

In general, the bulk of the diet should be divided into three equal meals Patients taking protamine zinc insulin should always have an additional meal at bedtime This is best arranged by dividing the carbohydrate in the diet 2 2 2 1/7 (2/7 for breakfast, lunch and dinner, with 1/7 given at bedtime) An occasional patient taking large doses of insulin requires a small between meal feeding to prevent hypoglycemia This can be arranged without upsetting total calories by eating a part of the next meal (such as bread, milk, or ... ahead of time It is often possible by such minor rearrangements to elim... disturbing peaks or drops in the blood sugar curve

TURNING FIGURES INTO FOO...

The problems here concern ... and measures, composition of foo... planning and substitutions An ... team can be built up by close coo... of physician and dietician consi... gether on the patient s problems ... scientious physician with plent... can do it all himself but most ... to have help from a dietician ... accurate and understands the pr...

0 5 Gm per lb body weight) Carbohydrate should be high enough to avoid significant ketosis and ketonuria, best not below 1 Gm per lb body weight Fat intake should be reduced to the minimum compatible with a palatable diet (30–50 Gm) Vitamin supplements are desirable, even though some patients complain that they stimulate appetite Weight reducing drugs are contraindicated

Undernourished Diabetics

In the undernourished patient especially if diabetes is severe or if infection or hyper thyroidism exists a large dietary intake may be necessary to induce a gai[n in] weight. In such cases the use of insuli[n is] mandatory, while a very liberal carbo[hy]drate intake is often desirable and help[ful.] Moderate glycosuria can be temporar[ily] disregarded unless there is some speci[al] reason to avoid it No restriction need [be] placed on fat or protein intake As th[e] weight approaches normal more accurat[e] control may be re-established, though the patient sometimes has difficulty in under standing why he must abandon for largely theoretical reasons a regimen on which he has felt so much better and freer

TABLE 32 MEASURES FOR DIABETIC DIETS

You may eat without measuring

Lettuce, Coffee, Salt, Vinegar
Mushrooms, Tea, Pepper, Spices
Saccharin, Water, Spices, Bouillon cubes
Clear broth from which the fat has been removed
Junket tablets may be used with the milk allowed in your d et

Group 1 vegetables

Eat a green leafy or yellow vegetable daily

Asparagus	Kohl rabi
Beans (string or wax)	Leeks
Broccoli	Okra
Brussels sprouts	Onions (boiled)
Cabbage (green white or red)	Poke
Cauliflower	Pumpkin
Celery	Radishes
Chard	Rhubarb
Chinese cabbage	Sauerkraut
Chicory	Spinach
Cucumbers	Sprouts
Dandelion greens	Squash (summer)
[E]ggplant	Tomatoes
[G]reen peppers	Turnip greens
[K]ale	Watercress

[Gro]up 2 vegetables

[Car]rots	
[Oni]ons (raw or baked)	Canned tomato soup
[Egg]er plant	Canned tomato juice
[Ruta]bagas	Turnips
	Hubbard squash

Cereal

Each portion listed is 1 serving Use whole grain cereal often

- ⅓ cup cooked oatmeal or pettijohn
- ⅓ cup cooked farina or cream of wheat
- ⅓ cup cooked wheatena or cornmeal
- ½ cup cornflakes
- ½ cup pep
- ½ shredded wheat biscuit
- ¾ cup bran flakes
- ¾ cup puffed rice
- 1 cup puffed wheat
- ⅔ cup wheaties
- ⅘ cup rice krispies

Fruit

Each portion listed is 1 serving Eat orange, grape fruit or tomato da ly

- 1 orange (medium size)
- ½ cup orange juice (scant)
- ½ *small* apple
- ⅓ cup unsweetened applesauce
- ½ grapefruit
- ½ cup grapefruit juice (scant)
- 1 cup tomato juice
- 1 large tangerine
- ⅓ cup pineapple juice (unsweetened)
- ¾ cup diced fresh pineapple
- 1 fresh pear (small size)
- 1 fresh peach (med um size)
- 1 cup strawberries
- 1 cup blackberries
- ⅔ cup black raspberries
- ⅔ cup red raspberries
- 2 fresh apricots (large s ze)
- ¼ honeydew melon (small s ze)
- ¼ cantaloupe (med um s ze)
- ½ to a 2" sl ce watermelon

[Ada]pted from out ne prepared by Eloise R. Trescher Nutrition Consultant, for use in the Diabetic Clinic of the Johns Hop[kins Ho]spital.

infection or injury such as a surgical procedure During illness it may be disastrous to stop insulin because the patient does not eat much The insulin requirement may have become so exaggerated that ketosis may set in almost immediately after the first missed injection

If blood sugar values are low, the patient may have to eat promptly after administration of insulin in order to avoid immediate hypoglycemia

Insulin is generally packaged in 10 cc vials containing 40 or 80 units of insulin per cc Distinctive labeling characterizes each insulin and each dosage strength An outline is presented in *New and Non Official Remedies,* a publication of the Council on Pharmacy and Chemistry of the *American Medical Association*

STANDARD INSULIN

This is a quick acting amorphous insulin preparation The insulin is administered subcutaneously fifteen to thirty minutes before meals The midday dose can usually be omitted without disturbing regulation Diet is generally arranged as outlined under the section of diets It usually is advisable to initiate insulin therapy with 10–15 unit doses of insulin before breakfast and dinner, this amount being increased gradually, if necessary according to the amount of sugar in the urine or blood

A rapid method for estimating insulin requirements can be employed The urinary output of sugar is tested in voidings three hours after meals and before breakfast standard insulin is given at this time according to the extent of glycosuria 10 units for a yellow or brick red reaction with Benedict s qualitative reagent (+++ or ++++) and 5 units for an olive or green reaction (++) The total insulin requirement thus can be approximated in a day or two A similar program of insulin administration according to individual voidings may be used after operation, or under other circumstances such as nausea and vomiting and diarrhea, where variations in food intake are temporarily unavoidable

SOLUTION OF ZINC INSULIN CRYSTALS

Solution of zinc insulin crystals is a preparation of crystalline insulin chemically combined with a trace of zinc. Not less than 0 2 mg or more than 0 4 mg of zinc are permitted per 1000 units of insulin This insulin is possibly longer acting than the standard variety and has a maximum effect at two to four hours after injection It is also possibly less antigenic than standard insulin and may be cautiously tried in instances of hypersensitivity to the latter However, its advantages are not sufficiently striking to have led to its widespread acceptance and usage It is provided in strengths of 40 and 80 units per cc Arrangements of diet, dosage and time of administration are similar to those for standard insulin

Standard insulin and solution of zinc insulin crystals are usually reserved for the following situations

1 The control of types of diabetes in which glycosuria occurs primarily after meals but fasting blood sugar is not very high
2 To suppress daytime glycosuria in patients taking a longer acting insulin
3 To control diabetes during acute situations (such as surgery or infection) when insulin requirements may change abruptly
4 For emergency use in diabetic acidosis

PROTAMINE ZINC INSULIN

One of the most commonly used slow acting insulin preparations is protamine zinc insulin Protamine is prepared from the sperm or mature testes of fish of the *Salmonidae* family Protamine, a small

is able to spend the time she can give the patient many pointers on selection, measurement, and preparation of food which few physicians understand at all.

The diets presented in Table 30 offer a general picture of the range of usual diabetic diets. The food is divided into three equal parts for the three meals. If the patient receives protamine zinc insulin a bedtime meal is added as indicated in Table 31. Tables 32 and 33 give the substitutions which allow variety in the choice of foods without too much variation in the total composition of the diet.

The accuracy with which the patient follows these instructions determines the evenness of regulation. Some improvement may be made by weighing rather than measuring the portions but this is tedious and usually unnecessary. Weights are misleading when there is much variation in water content or composition of foods but the use of weights avoids possible large errors in unit size, e.g., of a piece of fruit. With common sense training and a helpful spirit the patient can usually do very well with measures but it may be advisable for all patients to weigh their food during their initial training and during any subsequent period of unexplained glycosuria.

In the long run, the most important thing is for the patient to understand what the diet is supposed to do. Is it simply to reduce his carbohydrate and calori take? Here, slight daily variation is l less. Or is it to furnish him with ex the same amount of carbohydrate each so that his blood sugar can be kept nor with insulin? Here, accuracy must greater since either too much or too li carbohydrate is undesirable. If the patie is closely regulated, the danger is mu greater when the patient fails to eat h full quota at any meal than when he ea a trifle too much.

"Free" Diets

Finally, certain cases may be placed on a "free diet" to allow for weight gain. An active growing child or an undernourished, severe labile diabetic may be given a minimum amount which he must eat at each meal and allowed to eat what he pleases beyond this minimum quota. Insulin is adjusted only to allow weight gain and to avoid ketosis. Glycosuria is neglected when present while its absence serves as a warning of possible hypoglycemia. Some difficult cases who show hypoglycemic reactions and a poor weight gain on conventional diets are greatly improved by this regimen and seem to take a new lease on life. The use of such diets is increasing but generally only in children and in special adult cases until study of the long term results can be completed.

Types of Insulin

INSULIN is available in quick acting and arious slower acting forms. The original nsulin, now termed standard insulin, ecomes effective fifteen to thirty minutes ter injection and attains a peak effect in o to three hours. More recent prepara ns have been devised to delay absorption nsulin from the injection site to provide onstant titer of insulin during the twenty four hour period after injection. Thus it is frequently possible with these newer insulins to maintain effective control over the blood sugar with a single daily injection.

The physician must be cognizant of the decrease in insulin requirement which may occur with exercise and the sharp increase which may take place with intercurrent

infection or injury such as a surgical procedure. During illness it may be disastrous to stop insulin because the patient does not eat much. The insulin requirement may have become so exaggerated that ketosis may set in almost immediately after the first missed injection.

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A rapid method for estimating insulin requirements can be employed. The urinary output of sugar is tested in voidings three hours after meals and before breakfast; standard insulin is given at this time according to the extent of glycosuria, 10 units for a yellow or brick-red reaction with Benedict's qualitative reagent (+++ or ++++) and 5 units for an olive or green reaction (++). The total insulin requirement thus can be approximated in a day or two. A similar program of insulin administration according to individual voidings may be used after operation, or under other circumstances such as nausea and vomiting, and diarrhea, where variations in food intake are temporarily unavoidable.

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1. The control of types of diabetes in which glycosuria occurs primarily after meals but fasting blood sugar is not very high.
2. To suppress daytime glycosuria in patients taking a longer-acting insulin.
3. To control diabetes during acute situations (such as surgery or infection) when insulin requirements may change abruptly.
4. For emergency use in diabetic acidosis.

PROTAMINE ZINC INSULIN

One of the most commonly used slow-acting insulin preparations is protamine zinc insulin. Protamine is prepared from the sperm or mature testes of fish of the *Salmonidae* family. Protamine, a small

amount of zinc chloride, and standard insulin form a chemical complex which dissociates slowly after subcutaneous injection Insulin is absorbed from the local site and reaches the blood stream at a similarly slow rate The peak effect usually occurs four teen to sixteen hours after injection but may persist for eighteen to twenty six hours or longer Since there is generally a delay until an effect on blood sugar occurs protamine zinc insulin is usually given one half to one and a half hours before breakfast Occasionally the material is injected as an alternative method before the evening meal It is generally wise to begin regulation with ten to fifteen units of protamine zinc insulin increasing the dose daily at first However when control is almost gained each dose should be evaluated for several days before a change is made Occasionally reduction in dosage to initially inadequate levels may be necessary after the hyperglycemia has been overcome If a change is being made from standard insulin to protamine zinc insulin a dosage about half of that used with the standard insulin is given This is then increased as necessary

NPH INSULIN

NPH insulin is crystalline and represents a variation of protamine zinc insulin first advocated by Hagedorn The concentration of protamine and zinc is less in NPH than in protamine zinc insulin This permits an earlier peak of insulin effect than with protamine zinc insulin NPH insulin compares in activity to a 2 1 mixture of protamine zinc insulin and regular insulin The peak maximal effect usually occurs in seven to eleven hours after injection and may persist for twenty to thirty hours or longer

The great advantages of the longer acting insulins are stability and continuity of regulation Severe young diabetics are difficult and often erratic subjects to control on regular insulin Blood sugar values are subject to rapid changes with danger of development of intermittent ketosis and glycosuria A slower acting insulin often aids in the control of such patients permitting gain in weight and better hydration The slower acting insulins may also be used In patients who can tolerate them without development of early morning hypoglycemia these usually include diabetics of moderate severity in the younger and middle age groups (2) In the regulation of severe diabetics usually supplemented by regular insulin to control postprandial hyperglycemia and glycosuria

GLOBIN INSULIN

Another form of slower acting insulin is globin insulin with zinc This is standard insulin modified by the addition of purified globin from beef hemoglobin and zinc chloride The insulin is probably absorbed onto the protein Subcutaneous dissociation is slow and absorption from the injection site thus prolonged The peak effect occurs ten to twelve hours after injection and the effect may last in some for eighteen to twenty hours The proponents of this insulin point out that the peak effect and duration correspond more closely to the usual times for meals than can be obtained with protamine zinc insulin

The dosage and timing of injections are about the same as those with protamine zinc insulin The division of carbohydrate in the diet however is different for globin insulin it is divided into thirds and given at each of the three meals When a change over from standard or protamine zinc insulin to globin insulin is made about half the dosage of globin insulin is given initially This is increased to two-thirds the following day and then the dosage slowly adjusted as required

INSULIN MIXTURES

Comment has been previously made of the lag between the injection of the slow acting insulins and subsequent effect upon

blood sugar. This frequently may result in glycosuria after breakfast, although the *blood sugar may drop to levels causing* shock during the night. A separate injection of standard insulin before breakfast meets the requirement for a quick-acting insulin, but the need for two injections provides an objection to this practice.

The quick and slow components of insulin therapy provided by the concurrent injections of standard insulin and protamine zinc insulin have been shown to be preserved in mixtures of standard insulin and protamine zinc insulin given together as one injection. The efficacy of each insulin becomes reduced about 50 per cent as a result of mixing. Mixtures range in proportion from 1:1 to 1:2 of standard to protamine zinc insulin for patients with high insulin requirements to the reverse for patients with a daily requirement of less than about 40 units. Diet is generally arranged as for globin insulin, carbohydrate being divided into thirds and administered in equal amounts at each meal.

The standard insulin is generally drawn into the syringe first and then the protamine zinc insulin is added. Practice is needed to prevent contamination of the protamine zinc insulin bottle by the standard insulin in the syringe, and to insure accuracy of dosage.

Insulin Shock

AN OVERDOSE of insulin leads to a rapid decline in blood sugar. The normal blood level is 80–120 mg. per 100 cc. A reduction of sugar to 40 mg. per 100 cc. or less is generally accompanied by manifestations of insulin shock leading to coma and death if hypoglycemia is not *interrupted*. Conversely, a blood sugar level of 70 mg. per 100 cc. or above is presumptive evidence against the diagnosis if the blood was taken during an episode of shock. The rate of fall in blood sugar is also a factor in determining the blood level at which shock appears.

The administration of sugar is specific for the treatment of insulin shock. Shock is usually heralded by a sense of epigastric uneasiness, fatigue, weakness, and sweating. A lump of sugar or glass of orange juice taken at this point may forestall the later symptoms of mania, convulsions, and stupor, or often of sudden lapse into unconsciousness.

It is therefore wise for the physician to instruct the diabetic patient to carry sugar with him at all times. He should also advise the patient to carry an accessible identification card with name, address, and a statement that the patient is a diabetic taking insulin. This precaution may prevent another physician from injecting the patient with still more insulin in the event of unconsciousness from insulin shock but with a urine still containing sugar which was excreted during hyperglycemia several hours previously.

If the patient cannot swallow, 20–40 cc. of a 50 per cent solution of dextrose administered intravenously may be dramatic in its effect. However, the patient may relapse into shock and a liter or more of 5 per cent dextrose may be given as a hypodermoclysis, and injection of the more concentrated sugar solution may be repeated.

Epinephrine 1:1000, 0.5–1.0 cc. may be given subcutaneously as an emergency measure in insulin shock to raise the blood

amount of zinc chloride and standard insulin form a chemical complex which dissociates slowly after subcutaneous injection Insulin is absorbed from the local site and reaches the blood stream at a similarly slow rate The peak effect usually occurs fourteen to sixteen hours after injection but may persist for eighteen to twenty six hours or longer Since there is generally a delay until an effect on blood sugar occurs, protamine zinc insulin is usually given one half to one and a half hours before breakfast Occasionally the material is injected as an alternative method before the evening meal It is generally wise to begin regulation with ten to fifteen units of protamine zinc insulin increasing the dose daily at first However when control is almost gained each dose should be evaluated for several days, before a change is made Occasionally reduction in dosage to initially inadequate levels may be necessary after the hyperglycemia has been overcome If a change is being made from standard insulin to protamine zinc insulin a dosage about half of that used with the standard insulin is given This is then increased as necessary

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INSULIN MIXTURES

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weeks, and is often confused with the sudden blurring and diplopia which accompanies a hypoglycemic reaction

INSULIN RESISTANCE

Apparent resistance to insulin is occasionally found Several thousand units per day may fail to affect the blood or urinary sugar Lowell has demonstrated the presence of neutralizing antibodies in some patients These disappear upon cessation of insulin administration and reappear shortly after its resumption However, this mechanism is not present in all instances of insulin resistance and an explanation usually is lacking

Mild degrees of insulin resistance are noted in thyroid, adrenal and pituitary disorders, Cushing's syndrome, and acromegaly

INSULIN OVERSENSITIVITY

Failure of adrenal and anterior pituitary function is associated with oversensitivity to administered insulin A tenth of the amount required to produce shock in the normal person will precipitate the same result in the patient with Addison's or Simmonds' disease The same exaggerated insulin response may be noted in severe hypothyroidism or myxedema, in fatty liver and in hepatic disorders

*Diabetic Ketosis and Acidosis**

WHEN inadequate quantities of carbohydrate are available for storage and utilization, there is an overproduction of ketone acids from partial combustion of fat The appearance of ketone acids with sugar in the urine of a diabetic patient usually indicates a dangerous reduction in carbohydrate reserves and demands immediate treatment with insulin Ketonuria without glycosuria can be produced by severe carbohydrate restriction in normal or diabetic individuals In the diabetic, ketonuria without glycosuria is a rare occurrence except when caloric needs are increased by hyperthyroidism or infection In this case, the appearance of ketone acids calls for the administration of more carbohydrate, with enough insulin to ensure its storage and utilization

Heavy glycosuria and ketonuria are accompanied by a decreasing body weight which reflects both the loss of necessary foodstuffs and the loss of body water with its associated electrolytes—sodium, bicarbonate, and chloride from the blood plas
and interstitial fluid, and potassium, pl
phate, and protein from the cells As
excretion of the strong ketone acids dar
ously depletes the body s reserves of sod
potassium, and water, any slight upset
precipitate acidosis In this malnou
and depleted state, the patient is eas
to an infection, which is a frequen
of acidosis

SYMPTOMS

The appearance of marked p
and polyuria, weakness and so
should warn the patient that the
is dangerously out of control A
dosis becomes more marked
nausea, and vomiting appear,
accompanied by diffuse abdon
The odor of acetone on the bre
more obvious breathing becom
slow as acidosis leads to the
described by Kussmaul, the p
a curious cutaneous flush in
shocklike state of the circ

sugar by causing glycolysis in the liver It should not be used in the presence of liver glycogen depletion such as follows pro tracted vomiting

Prolonged coma from insulin shock may ead to cerebral anoxia and diffuse punctate emorrhages over the brain, an increased ll count in the spinal fluid and changes in the electroencephalogram The may be irreversible

Controlled deep insulin shock has used extensively in the treatment of sch phrenia The rationale is more or empirical Such therapy should be tempted only with experienced psychiat guidance

Other Reactions to Insulin

NODULE FORMATION

The injection of protamine zinc or globin insulin intradermally, instead of subcutane ously, may give rise to nodule formation The nodules may be painful areas several centimeters in diameter which may persist for several weeks In some individuals similar nodules may form after subcutane ous injection Globin insulin may be tried if this complication arises after protamine zinc insulin administration, and vice versa At times the slower acting insulins must be abandoned and standard insulin used The nodule is apparently an allergic re sponse to the insulin Breakdown of the nodules is rare but occasionally takes place

HYPERSENSITIVITY

Hypersensitivity to insulin most often the protamine form is quite frequent It is usually manifested a week or two after the first injection If the reactions are mild and localized, no special treatment is necessary since in most patients, the hypersensitivity ceases after the end of about one month If severe another brand of insulin may be tried Solution of zinc insulin crystals may e employed Occasionally, insulin derived rom a different species of animal may be quired If the reactions are systemic, such asthma or anaphylactic shock, epine rine, ephedrine and antihistaminic nts are indicated Desensitization, be ginning with a dose of 001 unit intra dermally and increasing slowly to 1 unit, is often successful

FAT TUMESCENCE AND ATROPHY

Diffuse persistent swelling and increase in fat over wide areas may occasionally re sult from insulin injection Little is known of this disorder

On the other hand, atrophy and almost complete disappearance of subcutaneous fat may occur in injected areas A common cause for this complication is use of the same site for injection This practice is unnecessary even with self injection The dorsal aspect of both thighs is available from within several inches of the inguinal ligament to within several inches of the patella where the suprapatellar bursa must be avoided The deeper blood vessels on the medial aspect of the thigh must also be avoided By rotation of the injection site and by the use of both thighs, the same injection place need be used only once a week However, fat atrophy may occur occasionally despite these precautions

DISTURBANCES IN VISION

This complication may follow rapid re duction in blood sugar values and is asso ciated with changes in the fluid content of the eye It occurs soon after treatment with insulin has begun and disappears in a few

ossible the quantity of insulin which will llow enough carbohydrate to be stored and burned, so that the excessive produc tion of ketone acids will be suppressed This amount varies greatly Most patients in acidosis require between 100 and 300 units of insulin Rarely as little as 50 or as much as several thousand units of insulin may be needed In view of this large vari ation in the necessary dose the program of treatment must be adaptable and the re sults must be closely followed since too little insulin results in a serious delay while too much insulin may lead to a serious hypoglycemic reaction Protamine zinc insulin is less effective than crystalline or regular insulin because of delayed action and tendency to late cumulative effects It is proper to give a severe diabetic his routine daily dose of protamine zinc in sulin but all supplementary insulin should be given in the regular form

Schedule The safest and most effective method of employing insulin is to give it at hourly intervals checking the urinalysis before each dose If the patient is unable to void he should be catheterized and the catheter left in place until voluntary co operation is possible The initial dose of regular insulin should depend to some ex tent on the severity of the pre-existing diabetes and of the acidosis The mild diabetic who would ordinarily take only a few units of insulin and whose acidosis is not marked may be given as little as 20 units of insulin each hour The severe diabetic who has gone into acidosis in spite of regular administration of insulin will obviously require much more insulin and should be given as much as 50 units of insulin each hour In the most severe cases of insulin resistance as much as 100 units of insulin may be given hourly but this should be done only after the patient has failed to respond to more moderate doses Acetone and diacetic acid should begin to ear from the urine within a few hours, although traces may be excreted for as long as twelve hours after the beginning of treatment A rapid fall in blood sugar or the disappearance of sugar from the urine calls for the administration of glucose to avoid hypoglycemia Between 10 and 50 Gm of glucose should be given intra venously each hour after the urine sugar shows evidences of decreasing or when the blood sugar has fallen to less than 200 mg per 100 cc Insulin and glucose should be given until the ketone acids disappear from the urine

Precipitating Cause

As soon as these emergency measures have been initiated every effort should be made to detect and eliminate any factors which may have contributed to the develop- ment of the acidosis In many patients the acidosis may be simply due to failure to take insulin If, however, acidosis has developed without withdrawal of insulin special care should be taken to search fo infection which is the next most commo reason for the development of acidosis T signs of the infection may be masked the severe dehydration Signs of pneumo may not appear until the patient is hydrated Fever is often minimal or ab during acidosis and leukocytosis is an reliable sign

The history is often of considerable and the family should be asked symptoms preceding the onset of a A respiratory infection is the com precipitating cause The sinuses a should be examined The pharyn be carefully inspected and a ches desirable if there is any suspicion monia Infection of the urinary tr common in diabetics Great care sary in the examination of the since an abdominal catastrophe during the development of acid giving the usual serious sym signs Localized abdominal ten

somnolence deepens to stupor and finally coma The blood shows hemoconcentration, leukocytosis, hyperglycemia, and a profound reduction in the carbon dioxide-combining power

TREATMENT

The treatment of diabetic acidosis may be divided into the following steps

Emergency

1 Treatment of circulatory collapse and profound acidosis
2 Administration of adequate doses of insulin

Immediate

3 Detection and treatment of infection or other precipitating cause
4 Specific treatment of other complications, such as gastric dilation

Intermediate

5 Administration of glucose as blood sugar falls
6 Replacement of potassium and phosphate if needed

Final

7 Re establishment of oral feeding
8 Determination of maintenance dose of insulin

Circulatory Collapse

Circulatory collapse must be treated promptly, since it is an immediate threat to life and interferes with the effectiveness of injected insulin A brisk intravenous infusion of isotonic solution of sodium chloride should be started as soon as the patient is seen A minimum of two liters should be given within the first four hours of treatment Further administration of saline should be gauged by the state of the circulation and of the patient s hydration Most patients will require considerably more than two liters, but older patients and repeated examinations of the lungs, heart, and neck veins to avoid the development of congestive failure or pulmonary edema under a large load of intravenous saline

Plasma Volume Occasionally the plasma proteins are so depleted that the replacement of sodium chloride and water fails to restore the plasma volume to normal Patients of this type fail to show the usual reduction in hematocrit under treatment with saline solutions, and circulatory collapse may persist or grow worse Such patients should be given plasma or albumin until the hematocrit falls and the circulation improves The use of whole blood is rarely necessary, but blood can be given if plasma or albumin is not available

Severe Acidosis If acidosis is severe, it is a good plan to give sodium lactate or sodium bicarbonate during the initial treatment It is usually not necessary or desirable to give more than 500–1000 cc of an isotonic solution of lactate (1/6 molar) or bicarbonate (1 3 per cent) The use of larger amounts of these alkaline solutions often leads to alkalosis and a reduction in the serum chloride concentration Since much base is liberated by the elimination of the ketone acids from the body fluids, it is best to give sodium lactate or bicarbonate only during the initial stages to cope with a severe acidosis and to withhold alkalies after the first few hours unless the carbon dioxide combining power fails to increase with routine therapy

Insulin

The need for insulin is as pressing as are the demands of the circulation When insulin is given subcutaneously, it may remain at the site of injection because of the severely impaired local circulation It may be helpful to give the first injection of insulin intravenously if the circulation is so depressed that proper absorption is unlikely

Dosage The aim of insulin treatment should be to give the patient as quickly as

ary to correct this abnormality As soon as the electrocardiogram reverts to normal and the muscular weakness is abolished the rate of administration of potassium should be reduced If the patient can take fluids by mouth the intravenous administration of potassium should be discontinued entirely and potassium citrate administered by mouth in doses of 3 Gm per hour for four doses after which the frequency and dosage may be reduced as the situation warrants If it is necessary to continue the intravenous administration of potassium a sharp lookout should be set for evidences of overdosage which may include generalized flushing and burning of the skin followed by muscular paralysis of a type practically indistinguishable from that caused by a low serum potassium The electrocardiographic changes of a high serum potassium are distinctively different from those caused by a low serum potassium so that the electrocardiogram is a valuable immediate method of detecting extreme variations in the serum potassium level When the serum potassium is too high the T waves become high and peaked the P wave may disappear and the QRS complex is widened and slurred into the high T wave

Chemical analyses of serum give a more reliable definition of the status and need for further treatment But if chemical supervision is not available in an emergency the electrocardiogram may be relied upon for interpretation of symptoms due to variations in serum potassium Rarely a patient may relapse toward a low serum potassium level after an inadequate intravenous dose of potassium This situation can be detected by the use of the electrocardiogram or by determinations of the level of the serum

The variable requirements of different patients and the critical nature of the serum potassium level make this phase of [illegible] ne of the most difficult in all medicine Some general rules should be followed Whenever possible, treatment should be given by mouth since much larger doses of potassium can be given safely by this route and since dangerous complications are much less likely to occur Intravenous administration of potassium is dangerous unless the rate of administration is carefully controlled Potassium salts should not be given to patients until the circulation is restored and until the urinary output is reestablished (except in the rare instance in which a dangerously low serum potassium has been demonstrated when cautious treatment is justified)

Oral Feeding

As the ketone bodies disappear from the
urine and the acidosis subsides the patient
generally regains a normal state of con
sciousness and begins to cooperate Som
hours may pass before the stomach
settled enough to accept food Oral feedin
should not be pressed on the patient un
he feels quite comfortable In the meantı
intravenous infusion of glucose is c
tinued at a slow rate When the pat
feels able to start eating again he sh
be given simple nourishments cons
largely of carbohydrate and a little pr
such as fruit juices broths tea, toast
or whatever he feels he can retai
effort should be made to put the
on regular meals until at least twe
hours after admission or until h
really hungry again

In the meantime the emphasi
be on giving enough carbohydr
250 Gm per day) to suppress the
of ketone bodies together wit
insulin to allow the retention a
tion of most of the sugar A
amount of glycosuria is harml
glycosuria should be avoided b
doses of insulin As soon as r
are started again the patien
placed on a diet as nearly as

nuscle spasm are not usual in acidosis, lthough diffuse tenderness and leukocytosis re common Meningitis occurs rarely but nay be exceptionally difficult to diagnose n the presence of coma In all of these questions an accurate history may give a aluable lead A detailed physical examina ion is imperative to detect signs suggestive of a localized infection Since generalized nfection with bacteremia may also occur asily in these debilitated patients a blood ulture is indicated if signs of an infection are present without definite localizing signs

General Care

The general care of the patient should not be neglected in patients with profound acidosis and coma Care of the mouth in surance of a clear airway by removal of mucus from the throat relief of gastric dilatation (because of the danger of aspira tion in an unconscious patient) and care of the bowel are all necessary If the patient is catheterized and especially if an indwell ing catheter is left in place every precau tion should be taken to avoid infection of the urinary tract

Blood Sugar

As the blood sugar falls under intensive insulin therapy it is common to observe that sugar disappears from the urine before the last of the ketone acids are eliminated Since the factor which suppresses ketosis is not insulin alone but rather the normal storage and utilization of carbohydrate it is desirable to give glucose at this juncture to replenish the body s depleted stores of carbohydrate Gastritis often delays or pre vents the absorption of carbohydrate given by mouth for many hours so that most physicians now use glucose intravenously at this stage The administration of glucose is indicated as soon as the blood sugar falls below 200 mg per 100 cc or glycosuria shows signs of diminishing The intra venous infusion of glucose should be rapid enough to keep traces of sugar in the urine and should be continued until the patient is able to take and retain carbohydrate by mouth

Serum Deficiencies

With the fall in the blood sugar toward normal and with the restoration of normal hydration and blood neutrality evidences of other deficiencies may appear in the diabetic patient The concentrations of potassium phosphate and amino acids which are usually elevated in diabetic acidosis may fall to subnormal levels in the serum when water, sodium chloride glucose and insulin are supplied

Hypopotassemia Since deficiency of potassium may progress rapidly to paralysis heart failure and even death it is advis able to measure the serum potassium after a few hours of treatment If the potassium level in the serum falls below 3 mEq /L (12 mg per 100 cc) generalized muscular weakness flaccid paralysis and respiratory failure frequently ensue

The appearance of these symptoms is accompanied by characteristic electro cardi ographic changes The T waves become low or inverted and the S T segment may be depressed The Q T interval is pro longed Variable A V block may be seen The paralysis may be generalized or ascending or it may involve the extremities or the muscles of respiration Pains and paresthesias are occasionally noted but sensory loss is uncommon Deep tendon reflexes are usually lost If chemical evi dence or clinical signs of potassium de-ficiency appear prompt treatment with potassium is necessary Three grams of potassium chloride (1000 cc of 0 3 per cent solution or 1300 cc of 30 mEq /L solution) should be administered slowly

The electrocardiogram and the state of the muscular tone and strength should be watched constantly There is great vari ability in the amount of potassium neces

regular insulin If the insulin requirement appears to be falling steadily, it is wise to anticipate the need for reduction of the protamine zinc insulin by a day of two since cumulative action may produce un pleasant and persistent attacks of nocturnal hypoglycemia For instance, if the fasting blood sugar falls from 200 to 150 and then to 100 on successive days there is a strong probability that a hypoglycemic reaction will occur on the next morning unless extra carbohydrate is given during the night It might have been better to reduce the dose of protamine zinc insulin sooner in this patient The presence of a trace of sugar in each urine specimen is a very comforting sign during a period of rapidly decreasing insulin requirement, and the appearance of a sugar free specimen may be taken as a warning in such an instance

When the insulin requirement has sta bilized the dosage and distribution of insulin is determined according to the usual method as already described

Complications Affecting Regulation of Diabetes

INABILITY TO TAKE FOOD

Inability to take food is met during gas trointestinal upset acute infection or in jury surgical or dental operation or briefly during roentgen ray examination of the gastrointestinal tract The mild diabetic who takes no insulin or only a few units may get by without food or insulin pro vided that his diabetes is not aggravated by the complication An increased insulin re quirement occurs almost without exception during pyogenic infections

The severe diabetic should be hospital ized promptly if he cannot eat properly as it is very difficult to avoid hypoglycemia or ketosis without some carbohydrate intake If the patient is out of reach of medical attention he should be instructed to reduce his insulin by about one half and to take frequent small amounts of carbohydrate in any form which can be retained If the pa tient can test his own urine, this should be done every few hours and small additional doses of insulin should be taken if glyco suria is heavy Meantime he should seek medical care as quickly as possible

Intravenous Feeding

... ent can then be given glucose ... is equivalent to the amount which he would have received by mouth at the time of each meal The rate of infusion should be adjusted so that th administration will be roughly comparab to the digestion and absorption of a me If the glucose is given too rapidly (m than 20 Gm an hour) a considerable p of the sugar may be lost in the urine sequently the blood sugar may fall to h glycemic levels as the insulin takes without any further absorption of sug any protamine zinc insulin is used time the patient must not be allo go for many hours at night without istration of glucose Since such a r or continuous infusion is annoyin usually best to use only regular during such an upset The patien be guarded however, from the ment of ketosis during the long period If such intravenous feedin sary for more than a day or two to supplement the simple gluc with such other nutrients as n cated The essential water solu salts and amino acids should b if intravenous feeding must for some days

the calculated diet on which he will be discharged so as to speed up his regulation The use of a submaintenance diet at this time is not advantageous Although a small carbohydrate intake may make it easier to control glycosuria it is likely to produce an unstable balance from which the patient slips easily into either hypoglycemia or ketosis It is better to give a full diet and to neglect minor degrees of glycosuria

Transition to Maintenance Regimen

The transition from the hourly regulation with regular insulin to the routine administration of insulin once or twice a day is one of the most difficult tasks which the physician is called on to perform It is most easily done by successive steps unless the acidosis has been so mild that the patient can quickly resume his previous status In the patient who has had a moderately severe bout of acidosis a large residue of insulin action is still present at the end of the initial phase of treatment when ketone acids disappear from the urine At this stage the frequency of insulin injection may be decreased from hourly intervals to intervals of three to four hours Injection of insulin is followed by the oral or intravenous administration of carbohydrate

The carbohydrate is given at a rate of about 10 Gm per hour, which may be increased if sugar disappears from the urine or if any evidence of hypoglycemia occurs Insulin dosage is adapted to the degree of glycosuria If the urine is free of sugar carbohydrate may be given without insulin or with only a few units If the urine contains large amounts of sugar, 20 units may be given If this dose proves inadequate to prevent heavy glycosuria and ketonuria it should be promptly and decidedly increased It takes only a few hours for such a newly regulated patient to slip back into acidosis, so that vigilance should be constant and treatment should be prompt and vigorous if any evidences of recurrence of ketosis are noted

As soon as the patient is able to eat he is regulated on regular insulin given before each meal If he has known diabetes and has been taking protamine zinc insulin before his attack of acidosis, he should receive his usual dose of protamine zinc insulin with supplementary injections of regular insulin before each meal As noted above, it is risky to maintain a patient in this state entirely sugar free during the first few days since his regulation is inclined to be erratic, while his insulin requirements may be falling Even when the urine contains sugar on most specimens hypoglycemia may occur suddenly and should be treated promptly with additional carbohydrate As the insulin is adjusted more accurately and peaks of heavy glycosuria are eliminated, the insulin requirement will usually decrease steadily over a period of one to three weeks

As the insulin requirement levels off, it may be advantageous to give some protamine zinc insulin in order to avoid overnight hyperglycemia or ketosis in a severe diabetic If the patient is on regular insulin alone and it is desired to substitute some protamine zinc insulin, approximately one third of the daily insulin is given as regular insulin in the morning together with an injection of protamine zinc insulin equivalent to the other two-thirds of the daily insulin dosage No further injections of regular insulin are given after the morning dose unless indicated by the urinalysis On the next morning the dose of crystalline insulin should be reduced if the pre breakfast urine specimen is clear of sugar

Further reductions in dosage are made according to the usual rules, a low blood sugar before breakfast calls for a reduction of dosage of protamine zinc insulin while hypoglycemia before lunch or during the afternoon indicates a smaller dosage of

regarded (lactosuria?) The blood sugar should be checked regularly

The patient should be informed without creating undue apprehension that to avoid the increased risks to herself and to the baby she must (1) follow directions on diet and insulin exactly and keep an accurate record of her urinalyses as instructed (2) have a check of her diabetes every two weeks more often if any upset is noted and weekly during the last trimester and (3) notify her physician of any upset or excessive glycosuria or ketonuria at once She should understand that mild glycosuria and sometimes traces of ketonuria occur very readily in pregnancy but that heavy or continuous excretion of sugar and espe cially of ketones calls for prompt attention

In the early months of pregnancy the nausea and vomiting may interfere with regular feedings If this presents any prob lem the patient should not receive a large dose of protamine zinc insulin since severe hypoglycemia may result if the patient is unable to eat Control may be maintained with multiple small portions of food at fre quent intervals covered by doses of regular insulin If vomiting is repeated or severe the patient should be hospitalized and fed intravenously as necessary until the worst of the upset has passed Hypoglycemia is a more frequent occurrence than acidosis at this stage but the balance may be difficult to maintain and the closest observation is necessary

The course of the middle trimester is usually smooth and uncomplicated but insulin requirements usually increase dur ing these months

The last trimester is most dangerous for the mother and for the fetus Toxemia of pregnancy is more frequent and more dan gerous though not necessarily more severe in the diabetic patient Large delicate babies are the rule difficult and delayed labor is common, and fetal death in utero occurs all too commonly without obvious cause Poor regulation of the diabetes in creases the hazard for both the mother and the baby

White believes that even with the most careful regulation a considerable number of diabetic mothers show an endocrine dis turbance which is related to the high inci dence of toxemia and of fetal mortality After the fifth month of pregnancy White states an increased blood concentration c gonadotropic hormone is a strong indica tion for the use of large doses of estrogen (stilbestrol 10 mg per day) and progestin (5 mg per day) These doses may be still further increased to a level of 30 mg of each daily at the end of pregnancy These suggested doses are very large and very costly The theoretical background is still not entirely clear but White s statistics are so impressive that they cannot be easily discounted Reports from other groups con firm the impression that large doses o estrogen are helpful in reducing the feta mortality

Toxemia of any severity is dangerous both mother and fetus If the toxemia pears to be progressive in spite of attempts at treatment pregnancy had l be terminated by cesarean section

Because of the high incidence of death during the last weeks of pregn the routine use of cesarean section at ous times after the thirty sixth wee been suggested It is not clear tha practice has resulted in any significa provement in fetal mortality Never if there is any evidence that the fet any trouble during the last week fetal size reaches the point where a labor seems likely it is probably induce labor or to perform a section

Delivery During delivery th tion of the diabetes may be quit It is probably best at this stage to lar insulin rather than prota insulin and to feed the patie

INCREASED INSULIN REQUIREMENTS

Increased insulin requirements may appear abruptly with the onset of an infection or with many other types of upset in the diabetic patient While the precipitating cause is being treated the dosage of insulin must be increased by the addition of extra doses of regular insulin given at intervals of one to six hours depending on the severity of the upset and on the state of control If heavy glycosuria and ketonuria are present the patient may be treated as if he were in acidosis If the situation is less acute 5 to 20 units of regular insulin may be given before each meal and again with some additional carbohydrate at bedtime the larger dose of insulin being given when glycosuria is heavy and smaller doses when only a moderate amount of sugar is present in the urine Minor degrees of glycosuria should be disregarded

Increased dosage of protamine zinc insulin gives more stability to regulation and prevents the overnight escape which is frequently seen in severe diabetes when regular insulin is not given between bedtime and breakfast But protamine zinc insulin has the disadvantage of slower action so that it may begin to reach its maximal effect just as the patient begins to improve when its residual activity leads to a strong tendency toward hypoglycemia It is always proper to give the patient his usual dose of protamine zinc insulin supplemented by increased dosage of regular insulin The use of increased doses of protamine should usually be reserved for less acute infections and complications like hyperthyroidism in which the physician can be relatively sure that the subsequent fall in insulin requirements will be slow enough to allow timely reduction of dosage

Carbohydrate intake should not be reduced below the usual dietary level during such periods of increased insulin need Stringent carbohydrate restriction is effective only in the mildest type of diabetes, but may actually make the handling of a severe diabetic more difficult during an acute flare up When fever or other causes increase the energy needs of the body, the patient may be helped by a more liberal carbohydrate quota than is usually given

PREGNANCY

Pregnancy provides a severe test of the regulation of diabetes, which can be met only by meticulous and continuous attention Maternal mortality has been unnecessarily high in diabetic mothers a situation which can be best corrected by the collaboration of the obstetrician and a physician with some experience in diabetic management Fetal mortality has been appalling but recent studies by White indicate that fetal survival may be greatly improved

The diagnosis of pregnancy calls for some adjustments and changes in routine treatment The diet must be increased to allow for a normal gain in weight unless the patient is considerably overweight calories are generally increased by 10 to 25 per cent The protein allowance should be liberal about 100 Gm per day for the patient of average weight and this allowance should not be reduced even in the presence of obesity An adequate intake of vitamins and minerals especially calcium and iron must be given by supplements if indicated

With these changes and increased demands of pregnancy most patients require insulin Patients who have taken insulin before pregnancy may find their requirements increasing from time to time these had best be determined from week to week Regulation should be adjusted to avoid marked hyperglycemia or hypoglycemia If necessary, small between meal feedings and a bedtime meal should be introduced Minor degrees of glycosuria should be dis

32. Nutritional Principles in Treatment

GRACE A GOLDSMITH

THE importance of nutrition in growth and development and in the maintenance of health has been increasingly recognized in recent years as a result of extensive research in this field Good nutrition is a vital factor in the prevention of disease and provision for adequate nutriture should be an integral part of the therapy of all pathologic states Malnutrition is etiologically related to many conditions other than the well known deficiency diseases while numerous disease states may be precipitating or conditioning causes of nutritional deficiency

General Principles in the Provision of Adequate Nutrition

IN ORDER to plan adequate nutritional therapy knowledge of the fundamentals of nutrition is essential Information concerning nutrient requirements for the maintenance of health and the influence of disease on nutrient requirement and utilization is of basic importance The physician must be familiar with the signs of nutritive failure and be skilled in evaluating the nutritional status of patients He then can apply his basic information in the light of clinical findings to formulation of therapy

It is the responsibility of the physician to teach his patient what is meant by an adequate diet in terms of ordinary foods to dispel false notions and prejudices concerning foods and to emphasize the importance of good nutrition in the maintenance of health When a patient requires a diet prescription it should be planned as carefully as a prescription for a chemotherapeutic agent It is unwise to use a standard printed or mimeographed form Instead an individualized regimen designed to meet specific problems should be prescribed The psychologic as well as the physiologic value of such a procedure can not be overemphasized In the art of medicine there is no more difficult problem than attempting to change dietary patterns

Dietary Supplements The mainstay of all nutritional therapy is food rather than specially prepared concentrates digests or

during the time when she is unable to take the usual nourishment by mouth The regulation should be checked at frequent intervals with urinalysis and blood sugar determinations The tests for urine sugar may be seriously confused at this stage by the appearance of lactose in the urine

During the days following delivery the diabetic mother presents certain special problems If the insulin requirement has increased very much during pregnancy, there may be a rapid fall in the insulin needs within a few days after delivery This decreased need for insulin must be anticipated by maintaining a slightly elevated blood sugar, by using crystalline rather than protamine zinc insulin, and by a careful watch for the development of symptoms of hypoglycemia

Lactation is often inadequate in the diabetic mother Considerable amounts of carbohydrate are lost in the milk and must be replaced in the diet

The infant of the diabetic mother is subject to increased neonatal risk The incidence of injury during labor is considerable in these large babies Asphyxia must be prevented by careful observation of breathing with removal of mucus and administration of oxygen when necessary Hypoglycemia of the newborn is probably less common than we have been led to believe in the past but it is still a good plan to give these children repeated feedings of glucose by mouth during the first few days of life The injection of glucose is somewhat more difficult but can be used if necessary It should be realized, however, that large subcutaneous or intramuscular injections of strong sugar solutions may produce severe local tissue injury, while the use of smaller doses has only a very temporary effect on the blood sugar

tities of other food. If a polyvitamin tablet is added to this regimen, most of the nutritive requirements of the average patient who has no complicating problems will be supplied.

In severe, protracted illness, nutrition becomes a much more serious problem. Suggestions for handling some of the many difficulties encountered will be discussed in the sections which follow.

EVALUATION OF NUTRITIVE STATE

Evaluation of the nutritional status of the individual patient is not a simple procedure. There are few pathognomonic signs of malnutrition. Furthermore, nutritive failure occurs gradually. The first abnormality is depletion of the tissue stores of a nutrient; this is followed by biochemical and physiologic abnormalities with impair

TABLE 35. STANDARD FOR EVALUATION OF DIETARY PATTERN

Foods Ordinarily Used, Type, Amount, and Frequency

Food group	*Amount recommended daily*	*Primary purpose*	*No. servings used per week*	*No. servings recommended per week*	*Difference + or −*
1. Vegetables, leafy green and yellow	1 serving (100 Gm. or ½ cup)	Hemicellulose, vitamin A, vitamin C, riboflavin		7	
2. Citrus fruit or juice (or twice the amount of tomatoes or juice)	1 serving (½ cup or 4 oz.)	Vitamin C		7	
3. Vegetables and fruits	2 or more servings (100 Gm. or ½ cup each)	Hemicellulose, iron, vitamin C, vitamin A		14	
4. Milk, whole (fresh or canned), skimmed, dried, or buttermilk	2 servings (1 cup or 8 oz. each)	Calcium, riboflavin, protein		14	
5. Lean meat, fish, poultry or 2 eggs*	1–2 servings (100 Gm. or 3½ oz. each)	Protein, thiamine, niacin, iron		7–14	
6. Enriched or whole grain bread and cereal	4–6 slices and 1 cup cooked cereal (one cup cereal = 2 slices bread)	Thiamine, niacin, iron, calories		28–42 slices and 7 cups	
7. Butter or fortified margarine	3–5 servings (1 pat or approx. 1 tsp. each)	Fat, vitamin A		21–35 servings	
Other energy yielding foods as sweets, pastries, unenriched bread and cereals, gravies, salad dressings, candy, sweetened carbonated and alcoholic beverages		Calories			

Food dislikes   Vitamin Concentrates or Tonics   Recent Change in Diet

Approximate Economic Status   Reliability of Information

Probably deficient in ________ ________ ________

* Cheese 3½ oz. or dried beans 1–1½ cups (cooked) may be substituted for meat twice weekly.

single nutrients Nevertheless, it is often necessary to add vitamin, protein, or mineral supplements to the diet to replenish depleted tissue stores, to treat manifest nutritional deficiency, or to supply extra nutrients required by the presence of disease

Supplements should be chosen in the light of the nutritional state of the patient and the pathologic condition which may be present If a patient has been eating a poor diet for years and there is reason to believe tissue stores of certain nutrients have been depleted, or if for any reason a patient cannot eat a well balanced diet, the missing factors should be prescribed Smaller quantities of individual nutrients are needed for maintenance of good nutrition than for replenishing tissue stores or reversal of pathologic changes The requirements of disease are considered in a later section (p 651) Here it is only necessary to point out that not only the disease but also the *patient must* be *studied*

Many preparations are available for dietary supplementation protein concentrates minerals and single or multiple vitamin capsules Suggestions as to the quantity of vitamins necessary for maintenance of adequate nutrition repletion of tissue stores and treatment of deficiency states are given in Table 34 If multiple vitamin supplementation is indicated, 1 capsule which contains the recommended daily allowances of these factors (Table 38) may be administered one to three times daily depending upon the patient s needs Capsules containing therapeutic doses of all the vitamins may be obtained, the approximate composition being vitamin A, 25 000 units, vitamin D, 1000 units, thiamine, 5 mg, riboflavin, 5 mg, niacinamide, 150 mg, and ascorbic acid, 150 mg To some of these preparations, folic acid, pyridoxine, and pantothenic acid have been added, while in others, yeast or liver concentrates have been included

If the therapeutic need is largely for vitamins of the B complex, brewers' yeast in the form of powder, tablets, or concentrates crude liver extract, or tablets containing the B complex vitamins may be prescribed

Supportive Nutritional Therapy Nutritional therapy in the ordinary types of brief illness not involving the gastrointestinal tract is relatively simple The patient *who has fever and anorexia should be* encouraged to eat a certain amount of food as this will hasten rehabilitation Liquid nourishment is usually more acceptable than solid food A useful mixture is one containing a cup of whole milk, 1 egg 2 tablespoonsful of skim milk powder, 1 tablespoonful of sugar, and vanilla flavoring This furnishes 350 calories and approximately 20 Gm of protein and may be given several times daily Most patients will also take fruit juice and small quan

TABLE 34 VITAMIN SUPPLEMENTS IN THERAPY
Daily Dosage

	For maintenance	*For replacement of tissue stores or increased requirement*	*For clinical deficiency states*
Vitamin A	5 000 I U	10 000 I U	20 000–100 000 I U
Thiamine hydrochloride	1–2 mg	5 mg	10–30 mg (or even 100 mg)
Riboflavin	2 mg	5 mg	10–30 mg
Niacinamide	10 mg	50 mg	100–500 mg
Ascorbic acid	50 mg	150 mg	300–1000 mg
Vitamin D	400 I U	1000 I U	1200–10 000 I U
Folic acid	0 5 mg (?)	2–5 mg	10–30 mg

TABLE 37 SYMPTOMS AND SIGNS SUGGESTIVE OF DEFICIENCY OF CERTAIN NUTRIENTS

Caloric deficiency
- Underweight and underheight
- Weight loss
- Wasting of tissues

Protein deficiency
- Growth retardation
- Weight loss
- Wasting of muscles
- Edema
- Hypoproteinemia

Vitamin A deficiency
- Photophobia
- Night blindness
- Xerosis conjunctivae
- Bitot's spots
- Dry scaling skin
- Follicular hyperkeratosis

Thiamin deficiency
- Burning soles of feet
- Numbness and tingling of toes
- Calf muscle tenderness
- Hyperesthesia or hypesthesia of feet and legs
- Loss of vibratory sense
- Absent patellar and Achilles reflexes
- Motor weakness (squat test)
- Edema
- Advanced polyneuropathy
- Beriberi heart disease
- Retrobulbar neuritis
- Central ophthalmoplegia
- Encephalopathic states

Riboflavin deficiency
- Photophobia, lacrimation burning, and itching of eyes
- Soreness of lips and tongue
- Circumcorneal injection and corneal vascularization
- Cheilosis
- Angular maceration and fissues
- Glossitis—purplish color, abnormalities of papillae
- Nasolabial seborrhea

Niacin deficiency
- Soreness and burning of tongue
- Chronic diarrhea
- Glossitis—redness, swelling, serrations abnormalities of papillae
- Pellagrous dermatitis
- Vaginitis and proctitis
- Mental changes—anxiety, hallucinations depression, disorientation, etc
- Encephalopathic states

Ascorbic acid deficiency
- Purpura, petechiae, and ecchymoses
- Red, swollen bleeding gums
- Perifolliculosis
- Poor wound healing

Vitamin D deficiency
- Frontal and parietal bosses
- Craniotabes
- Harrison's groove
- Enlarged costochondral junctions
- Enlarged joints
- Deformities of sternum
- Bowlegs or knock knees
- Osteomalacia

Vitamin K deficiency
- Hemorrhagic manifestations in jaundice or in the newborn

Folic acid deficiency
- Weakness and pallor
- Glossitis—redness, abnormalities of papillae
- Steatorrhea

Vitamin B_{12} deficiency
- Weakness and pallor
- Glossitis—redness, abnormalities of papillae
- Subacute combined sclerosis

Iodine deficiency
- Simple goitre

Iron deficiency
- Weakness and pallor
- Chronic glossitis

Dietary History

Unfortunately, too few physicians are familiar with methods of obtaining dietary histories One simple and useful procedure is to obtain a record of the kinds and approximate quantities of food eaten in the previous twenty four hours and to ascertain whether or not this represents the usual diet, or if some recent change in food habits has occurred As a check on the twenty four–hour dietary record, it is useful to have a list of foods, divided into several principal groups, and to determine how frequently the patient eats foods of each type These records may be evaluated by comparison with a standard a useful example of which is shown in Table 35 This simple method of evaluation will show the general quality of the diet as well as a rough quantitative estimate of food consumption If more detailed quantitative information is desired, tables of food values

TABLE 36 PHYSICAL SIGNS WHICH MAY BE ASSOCIATED WITH MALNUTRITION

Apathetic appearance

Hair—dry ' staring

Skin—facial
- Seborrhea, nasolabial
- Seborrhea other
- Erythema
- Folliculosis

Skin general
- Follicular keratosis
- Dryness and scaling
- Crackled skin
- Perifolliculosis
- Acneiform eruption
- Thick pigmented pressure points
- Purpura and petechia
- Bluish red cold extremities
- Pellagraform lesions
- Telangiectasis
- Redness of palms
- Nails brittle, flaking ridging

Eyes
- Conjunctiva thickened
- Bitot s spots
- Canthi fissures
- Circumcorneal injection
- Conjunctival injection
- Lids—blepharitis follicular hypertrophy

Lips and mouth
- Angular lesions
- Angular scars
- Cheilosis
- Pallor
- Ulcers of mouth

Tongue
- Papillary atrophy
- Papillary hypertrophy
- Patchy denuded areas
- Magenta colored
- Red tip and/or sides
- Fissures

Tongue (*Continued*)
- Erosions or ulcers
- Serrations and swelling

Teeth
- Caries
- Edentulous
- Dentures
- Fluorosis

Gums
- Marginal redness
- Marginal swelling
- Atrophy of papillae
- Recession with debris
- Bleeding

Thyroid
- Enlarged

Neuromuscular
- Calf tenderness
- Loss of AJ or KJ
- Plantar dysesthesia
- Motor weakness
- Vibratory sense lost
- Position sense lost
- Squat test

Skeletal
- Posture
- Frontal or parietal bosses
- Protuberant abdomen
- Harrison s groove
- Knock knees
- Bowlegs
- Enlarged wrists
- Enlarged costochondral junctions
- Flaring ribs
- Winged scapula
- Abnormality of sternum

Cardiovascular
- BP PR
- Heart—size
  - Rhythm
  - Murmurs
- Edema

ment of function and finally anatomic changes and obvious physical stigmata make their appearance Diagnosis in the early stages will depend on laboratory procedures and tests of metabolic function, and later, on clinical examination

The procedures which may be employed in the appraisal of nutriture are (1) a dietary history, (2) a medical history with particular attention to symptoms which may suggest nutritional deficiency (3) a clinical examination stressing the detection of signs which are known to be frequently associated with malnutrition, and (4) laboratory tests At times it is necessary to make tentative appraisal and attempt to substantiate the diagnosis by the response to therapy

TABLE 38 RECOMMENDED DAILY DIETARY ALLOWANCES*

Food and Nutrition Board, National Research Council, Washington, D C, REVISED, 1948

	Calories[1]	Protein (Gm)	Calcium (Gm)	Iron (mg)	Vitamin A[2] (I U)	Thiamine[3] (mg)	Riboflavin[3] (mg)	Niacin (nicotinic acid)[3] (mg)	Ascorbic acid (mg)	Vitamin D (I U)
Man (154 lb , 70 Kg)										
Sedentary	2400	70	1 0	12[4]	5000	1 2	1 8	12	75	[illegible]
Physically active	3000	70	1 0	12[4]	5000	1 5	1 8	15	75	[illegible]
With heavy work	4500	70	1 0	12[4]	5000	1 8	1 8	18	75	[illegible]
Woman (123 lb , 56 Kg)										
Sedentary	2000	60	1 0	12	5000	1 0	1 5	10	70	[illegible]
Moderately active	2400	60	1 0	12	5000	1 2	1 5	12	70	[illegible]
Very active	3000	60	1 0	12	5000	1 5	1 5	15	70	[illegible]
Pregnancy (latter half)	2400[5]	85	1 5	15	6000	1 5	2 5	15	100	400
Lactation	3000	100	2 0	15	8000	1 5	3 0	15	150	400
Children up to 12 yr[7]										
Under 1 yr[8]	110/2 2 lb (1 Kg)	3 5/2 2 lb (1 Kg)	1 0	6	1500	0 4	0 6	4	30	400
1–3 yrs (27 lb , 12 Kg)	1200	40	1 0	7	2000	0 6	0 9	6	35	400
4–6 yrs (42 lb , 19 Kg)	1600	50	1 0	8	2500	0 8	1 2	8	50	400
7–9 yrs (58 lb , 26 Kg)	2000	60	1 0	10	3500	1 0	1 5	10	60	400
10–12 yrs (78 lb , 35 Kg)	2500	70	1 2	12	4500	1 2	1 8	12	75	400
Children over 12 yr[7]										
Girls, 13–15 yr (108 lb , 49 Kg)	2600	80	1 3	15	5000	1 3	2 0	13	80	400
16–20 yr (122 lb , 55 Kg)	2400	75	1 0	15	5000	1 2	1 8	12	80	400
Boys, 13–15 yr (108 lb , 49 Kg)	3200	85	1 4	15	5000	1 5	2 0	15	90	400
16–20 yr (141 lb , 64 Kg)	3800	100	1 4	15	6000	1 7	2 5	17	100	400

* … to aim in planning practical dietaries The recommended allowances can be attained with a good variety … less well known … t applic … eriod will … mise that … tene has … the … actory in … orking at … amounts … plemental vitamin D … as well as for elderly persons … receding level … derate activity … 6 to 8 months. … n milk. … sed at present

may be consulted or the services of a dietitian may be enlisted.

Medical History

The medical history is important in detecting the presence of disease which may lead to nutritive defect and in eliciting symptoms which suggest the presence of nutritional deficiency. In childhood, a failure to grow or to gain weight, loss of appetite, lethargy, disinterest in play, or irritability suggests malnutrition. In adults easy fatigability, anorexia, photophobia, burning of the eyes, lacrimation, night blindness, burning of the tongue, soreness of the lips and angles of the mouth, bleeding gums, palpitation and dyspnea, gaseous indigestion, diarrhea, paresthesia, hyperesthesia or anesthesia of the fingers or toes, and easy bruising are complaints which may be related to nutritional deficiency. Each of these symptoms may occur in many pathologic conditions; hence all possible causative factors should be investigated.

Physical Examination

A number of physical findings often associated with malnutrition are given in Table 36. None of these signs is pathognomonic of nutritional deficiency but a group of findings occurring together is highly significant. Since malnutrition is usually associated with an insufficient supply of more than one nutrient, all types and combinations of signs may occur. The possible interpretation of certain groups of clinical findings is given in Table 37. Such interpretation should not be considered as absolute but may be clinically useful.

Laboratory Tests*

Laboratory tests which are of assistance in evaluating nutritional status include determination of hemoglobin concentration, erythrocyte count, and volume of packed red blood cells; estimation of the level of total serum proteins and of the albumin fraction; and measurement of the concentration in the serum, plasma, whole blood, or cellular components of vitamin A, carotene, ascorbic acid, riboflavin, and thiamine. Determination of serum iron and of calcium, phosphorus, and phosphatase in the blood may often be valuable. Estimation of chlorides, sodium, potassium, sugar, and ketones in both blood and urine are important in many conditions.

Correlation of findings obtained from the dietary history, clinical examination, and laboratory tests will usually enable one to determine whether nutritional deficiency is present as well as the severity and duration of the deficiency. Appropriate therapy then can be planned in the light of coexisting medical problems and their influence on nutritional state.

* See also Chapters 48 and 49.

Nutritive Requirements in Health

ANIMAL experiments have shown that some fifty to sixty different chemical substances are needed for growth and well-being. While not all of these nutrients are known to be required by man, sufficient information has been accumulated for many of them to permit formulation of standards for an adequate diet. Essential human nutrients include water, protein—which must contain eight or possibly nine essential amino acids—at least thirteen mineral elements, fifteen or more vitamins, and perhaps certain unsaturated fatty acids. In addition, the diet must furnish sufficient

TABLE 39 NORMAL DIET
(Approximately 2500 Calories)

Milk	2 cups
Cream	4 tablespoons
Egg	1
Meat, fish or chicken	2 servings 3 4 oz each
Potato, Irish	1 or more servings, ½ cup each
Vegetable	2 or more servings ½ cup each one green leafy or yellow and one raw
Fruit	2 or more servings ½ cup each one citrus
Bread and cereal, enriched or whole grain	5 servings
Butter or fortified margarine	2 tablespoons or more
Mayonnaise or salad dressing	1 tablespoon or more
Dessert	1 serving
Sugar	1 tablespoon or more

American cheese cottage cheese dried beans or milk may be substituted for meat or eggs one or two times a week

Other foods may be added to satisfy the appetite Use more milk another fruit or vegetable, or increase the size of servings

SUGGESTED MENU

BREAKFAST	NOON	NIGHT
Orange juice, ½ cup	Beef patty, 1	Pork chop, 1
Egg, 1	Cauliflower, ½ cup	Creamed potatoes ½ cup
Milk 1 cup	Bread 1 slice	Spinach, ½ cup
Cream 4 tbs	Butter 2 tsp	Lettuce and tomato salad 1 serving
Oatmeal ½ cup	Milk, 1 cup	Mayonnaise, 1 tbs
Bread, 2 slices	Peach 1	Bread 1 slice
Butter, 2 tsp		Butter, 2 tsp
Sugar as desired		Apple pie, 1 serving
Beverage if desired		Cheese, 1 oz
		Beverage if desired

mature and still births, congenital mal formations, and toxemias of pregnancy

Diet During Pregnancy The pregnant woman should include in her diet each day 1 quart of whole milk, at least ¼ pound of lean meat or equivalent (with liver once a week), 1 egg, 2 or more servings of fruit (including 8 ounces of orange juice or equivalent), 2 or more servings of cooked or raw vegetables (1 to 1½ cups including dark green leafy or deep yellow vegetables) a potato cooked in the skin legumes several times a week 4 slices of whole grain or enriched bread (½ cup of cereal is equivalent to 1 slice of bread), 2 tablespoonsful of butter or fortified margarine and 400 to 800 units of a vitamin D concentrate These foods will satisfy the recommended allowances shown in Table 38 Additional foods may be included to satisfy the energy requirement which may increase as much as 20 per cent in the last trimester of pregnancy Weight gain should be limited to 20 to 25 pounds Severe caloric restriction for weight reduction should not be attempted during pregnancy since it is difficult to obtain the necessary protective foods with an intake of less than 2000 calories

During lactation the energy requirement may increase 50 per cent above normal and the protein and calcium requirements are higher than those of pregnancy An extra pint of milk should be included in the diet with liberal amounts of vegetables and fruits

energy for metabolic needs, largely through carbohydrate and fat, and a small quantity of roughage

The Food and Nutrition Board of the National Research Council has formulated quantitative recommendations for the intake of certain nutrients the amounts varying with age, sex, and degree of physical activity (Table 38) These allowances represent the quantities which would appear desirable for the maintenance of good nutrition rather than minimal requirements Provision for a margin of safety is advisable to cover individual variations and to permit additional benefits, including a reserve supply for periods of stress These allowances should be used as objectives in planning adequate diets They are somewhat higher than average requirements but less than the amounts needed to compensate for depletion or to fulfill needs in pathologic conditions

Daily Diet These recommended allowances may be met if the following foods are included in the diet each day (1) one or more servings of green leafy or yellow vegetables, (2) one or more servings of citrus fruit, tomatoes or raw green cabbage, (3) two or more servings of potatoes and other vegetables or fruits (4) two or more cups of milk for an adult, three or four cups for children, (5) one to two servings of meat, poultry, fish, eggs, dried peas, or beans, (6) several servings of bread, flour, or cereals which should be whole grain enriched or restored, (7) butter or fortified margarine, and sufficient other foods to provide the necessary caloric intake Division of foods into the above seven basic groups is of assistance in planning and evaluating diets (see Table 35) Table 39 gives an illustrative diet which will furnish 2500 calories and will satisfy the recommended allowances of nutrients for an adult

During periods of physiologic stress, such as growth, pregnancy, and lactation, more of the 'protective foods are needed for adequate nutrition and it is in these conditions, in the absence of disease, that nutritive failure is most apt to occur If children fail to receive an adequate diet, growth and development are seriously retarded The importance of an abundant supply of protein calcium, iron, and vitamins during pregnancy has been clearly demonstrated in recent studies A good diet during this period is associated with a decrease in maternal and infant mortality and morbidity, and a diminution in the incidence of pre

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SALT The needs for salt and for water are closely interrelated A liberal allowance of sod [illegible]

PHOSPHORUS. Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation In the case of other adults the phosphorus allowances should be approximately 1 5 times those for calcium In general it is safe to assume that if the calcium and protein needs are met through common foods the phosphorus requirement also will be covered because the common foods richest in calcium and protein are also the best sources of phosphorus

COPPER The requirement for copper for adults is about 1 2 mg daily Infants and children require approximately 0 05 mg per kg body weight. The requirement for copper is approximately one tenth that for iron A good diet normally will supply sufficient copper

VITAMIN K. The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and for the first few days after birth Supplemental vitamin K is recommended during the last month of pregnancy When it has not been given in this manner it is recommended for the mother preceding delivery or for the baby immediately after birth.

FOLIC ACID Evidence for recognizing folic acid (pteroylglutamic acid vitamin B_c, *L. casei* factor or vitamin M) as an essential human nutrient is presented in the text. The quantitative requirement cannot be closely estimated from evidence now available

primary consideration will be replacement of fluid and electrolytes In chronic conditions where it is necessary to restrict the intake of certain foods for long periods of time the problem is more complex The use of small, frequent feedings and of concentrates and digests, orally and parenterally, will assist in supplying all the essential nutrients

DISEASES WHICH INTERFERE WITH THE UTILIZATION OF NUTRIENTS

Hepatic disease, hypothyroidism, advanced renal disease leukemia, and neoplasia are some of the conditions which affect the utilization of nutritive materials Changes in tissue metabolism may occur as a result of endogenous or exogenous toxins, following radiation therapy, and with the administration of certain drugs, such as the sulfonamides and antibiotics Severe injuries (wounds burns fractures etc), shock, and chronic anoxemic states have a profound effect on metabolic processes In *many of these conditions it is impossible* to restore adequate nutrition until the primary disease has been eradicated or controlled, or the therapeutic agent discontinued In some instances, increasing the supply of certain nutrients is of great importance For example, liver function may often be improved by diets high in protein carbohydrate, and the B vitamins particularly those factors having lipotropic activity Following severe trauma to tissue the administration of extra protein vitamins of the B complex, and ascorbic acid is often beneficial

DISEASES WHICH AFFECT THE EXCRETION OF NUTRIENTS

Diseases associated with polyuria such as diabetes mellitus, or diabetes insipidus as well as therapeutic diuresis, may cause loss of nutrients particularly vitamins from the body Occasionally, the excretion of dietary factors may be influenced by the administration of drugs Excessive sweating leads to an increase in the loss of sodium *chloride from the body*

Calories in Nutrition

CALORIC undernutrition and overnutrition are among the most frequent and important clinical problems Proper caloric allowance for adults may be considered to be that which will maintain ideal weight over long periods of time and, for children, that which will permit normal growth Unfortunately, neither ideal weight nor the optimal rate of growth is known It is customary to compare weight with standard charts which show average weight for height in relation to age and sex Such standards are far from precise even when allowance is made for body build* In adults, ideal weight may be considered to be the average weight at specific heights of individuals of age 25 who are in good health In evaluating growth rate, either the Wetzel grid or the charts employed by the Harvard and Iowa groups are preferable to other standards

* See also Chapters 15 and 31

ESTIMATION OF CALORIC NEEDS

Calculation of the daily energy requirement of an individual is neither simple nor exact Nevertheless an estimation can be made by consideration of the basal metabolism, plus the physical activity Basal metabolism is dependent on bodily size age sex, activity of the thyroid gland environmental temperature, and previous

Nutritive Requirements in Disease

DISEASES WHICH INCREASE NUTRITIVE REQUIREMENTS

Nutritive requirements are increased in many diseases particularly in febrile illnesses and in other conditions in which there is a rise in basal metabolic rate In fever, basal metabolism increases 7 2 per cent for each degree of rise in body temperature (Fahrenheit) Congestive heart failure, leukemia, and polycythemia are often associated with an elevation of metabolism and a tremendous increase may occur in hyperthyroidism The abnormal physical activity associated with delirium and certain psychoses also increases total metabolic needs These increased energy requirements must be met by additional calories and larger amounts of the specific nutrients concerned in metabolic processes of which the B vitamins are particularly important Loss of weight is usual in prolonged febrile illnesses and in thyrotoxicosis while clinical signs of deficiency of thiamine, riboflavin, and niacin are common in these conditions In the presence of infection the requirement of ascorbic acid appears to be increased and signs of deficiency of this vitamin may occur Abnormally high environmental temperatures increase the need for salt and symptoms of salt deficiency will appear unless an adequate supply is provided

ISEASES WHICH INFLUENCE GESTION, DIGESTION, AND BSORPTION OF NUTRIENTS

Diseases which interfere with the inges n, digestion, or absorption of food are ortant causes of malnutrition and pre many therapeutic problems Ingestion be interfered with in all of the many itions associated with anorexia indi on, nausea or vomiting such as gastrointestinal disorders, diseases of the biliar tract, infectious diseases, neuropsychiatric disturbances, chronic alcoholism, congestive heart failure and neoplasia Loss of teeth and poorly fitting dentures often lead to diminished food intake Food allergy is at times a limiting factor The use of therapeutic diets which are deficient in certain nutrients, may lead to serious malnutrition if continued for long periods of time

Improper digestion and absorption of food may occur when gastric, pancreatic, biliary, or intestinal secretion is defective, and in hypermotility of the gastrointestinal tract Poor absorption is the rule in inflammatory lesions of the intestine such as ileitis, ulcerative colitis, and the dysenteries in the steatorrheas in edema of the gastrointestinal tract, such as occurs in congestive heart failure or hypoproteinemia and following surgery in which part of the absorptive surface has been removed or ceases to function Achlorhydria or the administration of alkali liquid petrolatum, or adsorbents may also interfere with nutrient absorption Since the intestinal bacteria are responsible for the synthesis of a number of vitamins, the use of chemotherapeutic agents and antibiotics may inhibit such synthesis and possibly be a contributory factor in precipitating deficiency states

Some foods have been shown to contain antagonistic substances which combine with render unabsorbable, or destroy essential dietary factors Further studies along this line may explain the occurrence of nutritional deficiency in certain instances in which the diet appears to be adequate

In acute diseases of short duration such as gastroenteritis due to food infection the

young adults, full recovery may occur with proper care, *if more than 40 per cent, the* outlook is serious although recovery is at times possible

Treatment

The treatment of caloric undernutrition involves, primarily, supplying an abundance of calories The oral administration of *small amounts of food* at frequent intervals is the basis of therapy Easily digested foods, including milk, eggs meat fresh fruit, and cereals should be prescribed In severe uncomplicated starvation the diet should not be too abundant at first, perhaps 1800 calories, this being gradually increased The intake of fat should be limited since severe and sometimes fatal gastrointestinal disturbances may follow its administration If the patient will not eat satisfactorily he should be fed by stomach tube Parenteral feeding should be used *only when absolutely necessary In severely* starved persons the intravenous administration of large amounts of fluid is dangerous A sudden increase in plasma volume may precipitate circulatory failure

In caloric deficit associated with diarrhea a bland diet, low in residue, should be prescribed (Table 40) In hypermetabolic states, *the* caloric intake should be sufficient to meet the total daily energy requirement, with an excess to compensate for previous loss of tissue The foods used should be concentrated and of high energy *value The schedule shown in Table 41*, may serve as an example Vitamin supplements are usually indicated because of the importance of many vitamins, especially of the B group, in metabolic processes In the *absence of signs of vitamin deficiency*, a multivitamin capsule containing the quantities of these factors recommended for maintenance of good nutrition should be given two or three times daily If obvious deficiency exists, therapeutic doses should be administered (see Table 34)

TABLE 40 LOW RESIDUE DIET
(Approximately 2800 Calories)

	FOLLOWING FOODS SHOULD BE EATEN EVERY DAY
Milk	1 quart (Boiling milk may assist tolerance in certain patients)
Meat	2 large servings (1/5 *pound each) of lean fresh meat boiled, broiled or roasted* not fried Beef veal lamb, chicken or liver may be used Cream cheese eggs or tender fish may occasionally be substituted for meat
Irish potato	1 serving (½ cup or 1 medium potato)
Eggs	*2 at least, soft boiled or poached, not fried*
Vegetables	2 servings (½ cup each) All vegetables must be cooked and puréed (sieved) The following may be used carrots beets greens snap beans green peas tomatoes squash
Fruits	3 servings (½ cup each) fresh strained orange juice, very ripe mashed banana or any cooked strained fruit
Cereals	1 serving Grits, strained oatmeal (½ cup) or cornflakes (1 cup) No *cereals containing* bran
Bread enriched white	1 or more slices with each meal No rye or whole wheat bread
Butter	4 tablespoons or more as desired
Desserts	Only simple puddings as cornstarch, tapioca, custard jello ice cream
	GENERAL INSTRUCTIONS

All foods should be simply prepared and no fried foods should be included
The following foods should be entirely omitted pickles olives relishes highly seasoned foods salt pork pickled pork, sausages or lunch meats raw vegetables or fruits except strained orange juice and ripe banana

nutritional state In the absence of disease, basal metabolic needs may be calculated by reference to appropriate tables or the individual metabolic rate may be determined With the usual standards, variations of +5 to −20 per cent may be considered to be within the normal range A person resting quietly in bed will need 10 per cent above the basal requirement if the person is moderately active in bed the increase should be 30 per cent if out of bed and moderately quiet about the room 50 per cent according to Du Bois Caloric recommendations for normal persons engaging in various amounts of physical activity are included in the table of allowances suggested by the Food and Nutrition Board (Table 38) and in the report of the Committee on Caloric Requirements of the Food and Agriculture Organization of the United Nations

The ideal proportion of calories which should be obtained from protein fat and carbohydrate is unknown In the average diet in this country protein supplies about 15 per cent of the calories the remainder being divided about equally between fat and carbohydrate In calculating the energy value of food protein and carbohydrates are considered to furnish 4 calories per Gm fat 9 calories per Gm

A continual loss greater than 10 per cent of ideal weight may be considered indicative of caloric deficit Weighing a patient at frequent intervals is the best way to determine caloric adequacy or deficiency although in acutely ill patients fluctuations may represent changes in fluid rather than in the protein and fat content of the body

CALORIC UNDERNUTRITION AND STARVATION

Contributory Causes

Caloric undernutrition is a complication of many diseases particularly those in which anorexia is a prominent finding and those associated with an increase in metabolic rate Anorexia is common in the presence of prolonged febrile illnesses neoplasia chronic heart failure, advanced renal or hepatic disease and in many aged individuals Basal metabolism is increased in fever and hyperthyroidism and is often elevated in polycythemia vera, leukemia acromegaly, and in heart or lung diseases with severe dyspnea In acute infectious diseases and following surgical operations or serious injuries, temporary undernutrition is observed Calories are lost in the stools in diarrheal diseases and such loss may be extreme in steatorrhea In diabetes mellitus glycosuria is a manifestation of caloric loss

Diagnosis

Caloric undernutrition is often associated with a deficiency of protein and in all instances the nitrogen balance is negative Clinical findings are influenced by the previous state of nutrition the character of the diet and the type of disease complicating the clinical picture When caloric deficit occurs in association with hypermetabolism the findings are primarily weight loss wasting of muscles, weakness, and lethargy, in addition to the manifestations of the primary disease

In *starvation* unaccompanied by intercurrent disease the outstanding manifestations are extreme wasting fatigability, weakness syncope apathy hypotension bradycardia and edema There is a high incidence of physiologic sterility and amenorrhea If protein deficiency is associated edema and anemia are prominent findings Signs of vitamin deficiency occur only if the diet has been poor from a qualitative standpoint In severe prolonged undernutrition there is a decrease in basal metabolic rate The fasting blood sugar may be low and the tolerance for glucose diminished The prognosis is closely related to the degree of weight loss If the loss is 30 per cent or less in previously healthy

Protein in Nutrition

FUNCTION AND REQUIREMENT OF PROTEIN

Proteins are essential components of all cells and are constituents of all body fluids except bile and urine Consequently they are important for growth and for the maintenance of structure and function Recent studies have demonstrated that since cellular protein is constantly being broken down and reconstituted, a constant supply of essential amino acids must be available Rose and others have shown that man requires at least eight amino acids leucine, isoleucine, lysine, tryptophan phenylalanine, methionine, threonine, and valine Amino acids are important in the formation of specific cellular proteins and of special proteins such as hemoglobin fibrinogen, serum albumin and globulin A number of hormones are proteins or protein derivatives, while many enzymes have the property of proteins Proteins are important in immunologic and antigenic reactions They have a vital role in maintaining the fluid balance of the body and in regulating the osmotic relations between blood and tissues and between cells and intercellular fluids Proteins which are not utilized for specific functions are deaminated by the liver and used for energy

The recommended daily intake of protein is 1 Gm per kg body weight for adults and larger amounts during the period of growth and in pregnancy and lactation This protein must provide all the essential amino acids or synthesis of tissue protein will be limited and protein deficiency will result

PROTEIN DEFICIENCY

Protein deficiency is usually associated with an inadequate supply of calories and often of vitamins Numerous conditions other than starvation or an inadequate diet are contributory causes of protein deficiency The most important of these are (1) chronic febrile illnesses, thyrotoxicosis, and other hypermetabolic states which increase protein requirement (2) nephritis with albuminuria, effusions into serous cavities, draining sinuses weeping wounds, hemorrhage, and other conditions associated with loss of protein from the body (3) chronic diarrheal states or other disturbances interfering with digestion and absorption, (4) metabolic diseases as diabetes mellitus and (5) diseases of the liver which influence protein utilization

Nitrogen Balance When a person is put at bed rest, nitrogen balance becomes negative even in the absence of disease Following trauma such as fractures burns and operative procedures, there is a loss of nitrogen from the body which may amount to 0 6 Gm per kg body weight per day and may persist for long periods *It is difficult* and usually impossible to produce a positive nitrogen balance in these conditions even with a tremendous intake of protein In persons whose tissues have not been previously depleted it is probably unnecessary to obtain a positive nitrogen balance If serious depletion has occurred such an attempt is justifiable and may be life-saving

Clinical Manifestations

The clinical findings in protein deficiency are loss of weight wasting of muscles weakness edema and anemia The nitrogen balance is negative and there is a decrease in serum proteins particularly in the albumin fraction The normal concentration of serum proteins ranges from 6 to 8 Gm per 100 cc, that of serum albumin from 4 to 5 5 Gm There is not a given level of

TABLE 41 HIGH CALORIE, HIGH-PROTEIN DIET
(155 Grams Protein, 3500 Calories)

Food	*Amount*	*Approximate protein content* (Gm)
Milk	5 cups	41.0 (8.2 per cup)
Milk powder, *skim**	6 tablespoons	15.0 (2.5 per tbs)
Cream	½ cup	3.2 (0.4 per tbs)
Eggs	3	19.2 (6.4 each)
Meat, fish or chicken	2 large servings	
or	*4 oz each*	46.4 (5.8 per oz)
American cheese	1 serving, 2 oz	
or	or 2 cu in	
Dried beans	1 cup, cooked	
Potato	1 serving, ½ cup	
	or 1 medium	2.0
Vegetable	3 servings, ½ cup each	4.5 (1.5 per serving)
Fruit or juice	2 servings, ½ cup each	2.0 (1.0 per serving)
Bread and cereal enriched or whole grain	5 servings	11.3 (2.1 per slice bread) (2.9 per serving cereal)
Crackers	4	2.4 (0.6 each)
Peanut butter or cheese	2 tablespoons	7.8 (3.9 per tbs)
Butter or fortified margarine	2 tablespoons	
Salad dressing or oil	1 tablespoon	
Dessert	1 serving	3.0
Sugar	2 tablespoons	

SUGGESTED MEAL PLAN

Breakfast	*Noon*	*Night*
Fruit or juice, ½ cup	Meat, 1 serving	Meat, 1 serving
Eggs, 2	Green leafy vegetable, ½ cup	Potato, ½ cup
Milk, 1 cup*	Bread, 2 slices	Vegetable, ½ cup
Cream, ½ cup	Butter, 2 tsp	Salad, ½ cup
Cereal, 1 serving	Milk, 1 cup*	Salad dressing (oil) 1 tbs
Bread, 1 slice	Fruit, ½ cup	Bread, 1 slice
Butter, 2 tsp		Butter, 2 tsp
Sugar, 3 tsp		Dessert, 1 serving
10 00 A M	*3 00 P M*	*Bedtime*
Milk, 1 cup*	Eggnog†	Milk, 1 cup*
		Crackers, 4
		Peanut butter, 2 tbs

* Add 1 tablespoon of skim milk powder to each cup of whole milk
† See Table 45

CALORIC OVERNUTRITION

Caloric overnutrition is as important as caloric deficit The hazards of obesity are many and are discussed in detail in Chapter 33 In most instances, obesity is the result of simple overeating, the caloric intake being greater than the energy expenditure Caloric restriction is the most important aspect of therapy When diets containing less than 1200 calories daily are prescribed, supplements of vitamins and minerals (especially calcium) are necessary in order to insure qualitative adequacy

TABLE 43 HIGH PROTEIN, FULL-LIQUID DIET
(*120 Grams Protein, 2400 Calories*)

Milk	5 cups
Milk powder, skim*	10 tablespoons
Cream	½ cup
Eggs	3
Cereal, cooked	1 cup
Fruit juice	2 cups
Fruit, cooked, sieved	½ cup
Tomato or mixed vegetable juice	1½ cups
Gelatin	1–2 tablespoons
Butter	3 tablespoons
Dried brewer's yeast	3 tablespoons
Sugar	3 tablespoons

SUGGESTED MENU

Breakfast

Fruit juice 1 cup
Cereal, 1 cup
Butter, 2 tbs
Milk,* 1 cup

Noon

Milk soup, 1 cup
Fruit gelatin, 1 serving
Cream, ½ cup
Fruit juice, 1 cup
Butter, 1 tbs

Night

Tomato gelatin 1 serving
Custard, 1 serving
Milk,* ½ cup

10 00 A M

Eggnog†

3 00 P M

Mixed vegetable juice, 1 cup
Dried brewer's yeast, 2 tbs

8 00 P M

Eggnog†

Tomato Gelatin

Tomato juice ½ cup
or tomatoes canned sieved ½ cup
Gelatin, 1 tbs
Dried brewer s yeast, 1 tbs
Salt, ½ tsp
Water, ½ cup
Chill and serve

Fruit Gelatin

Gelatin, 1 tbs
Fruit cooked, sieved, ½ cup
or fruit juice, ½ cup
Sugar, 1 tbs
Water, ¾ cup
Chill and serve with cream, ½ cup

Milk Soup

Milk ½ cup
Milk powder, skim 1 tbs
Any cooked sieved vegetable, ½ cup
Salt as desired

Eggnog†

Milk, 1 cup
Milk powder, skim, 2 tbs
Egg, 1
Sugar, 1 tbs
Vanilla as desired

* Add 2 tablespoons skim milk powder to each glass of milk
† Eggnog will furnish 350 calories and may be frozen and served as ice cream or baked or cooked in double boiler until thick to make custard

drinks, tomato juice, soups, mixed dishes and bakery products A full liquid diet which includes concentrates is outlined in Table 43

Tube Feeding Tube feeding must often be used to increase the protein intake to the desired level Such feeding may be the sole method of therapy but preferably is given between meals and at night In most instances patients will tolerate 100–200 cc at a time, the tube being aspirated prior to each feeding A number of formulas suitable for tube feeding have been devised, one of which is given in Table 44 It is possible to furnish 300 Gm or more of protein by a combination of diet and supplementary oral or tube feeding

Protein Hydrolysates

The value of protein hydrolysates and the indications for their oral and parenteral use have been the subject of much study

either total serum protein or albumin at which clinical edema occurs This might be anticipated in view of the multiple factors influencing edema formation While nutritional edema is often due, in part to a decrease in the osmotic pressure of the serum proteins this is not the sole explanation It has been suggested that in starvation changes in tissue structure and elasticity may be etiologically important in edema formation

Determination of total circulating serum protein by estimating the blood volume as well as the concentration of protein in the blood may be valuable in detecting hypoproteinemia at an early stage The blood volume is often reduced in undernutrition and hemoconcentration is frequently noted in conditions associated with protein depletion Determination of the percentage of body weight lost is of value in estimating the severity of protein deficiency although edema may partially mask such loss

Treatment

Whenever possible protein deficiency should be treated by oral feeding The diet should be high in protein and also in carbohydrate so that sufficient calories are available to meet energy requirements Protein will thus be spared for restoration of hemoglobin serum albumin and other essential body proteins

Therapeutic Requirements of Protein The amount of protein to be prescribed is dependent on the degree of tissue depletion and whether there is continued loss of protein from the body To determine the desirable daily intake the quantity which is being lost should be added to the requirement for maintenance and then extra protein provided to replace body stores The maintenance requirement of protein is usually between 0 5 and 1 Gm per Kg body weight per day As previously noted nitrogen loss following severe injury may amount to 0 6 Gm nitrogen (3 75 Gm protein) per Kg per day The loss in exudates and transudates may be measured Elman calculates the amount of protein needed to replenish bodily stores by assuming that a decrease of 1 Gm in circulating plasma albumin represents a loss of 30 Gm of tissue protein Normal plasma volume may be estimated as about one twentieth of body weight Elman also calculates that about 50 per cent of ingested protein will be utilized Such calculations provide only a rough estimate of protein depletion and the assumed relationships do not hold under all circumstances

TABLE 42 PROTEIN CONCENTRATES FOR ORAL ADMINISTRATION

	Approximate protein content (%)
Corn germ	20
Wheat germ	25
Dried milk skim	35
Soybean flour	45
Dried brewer s yeast	45
Peanut flour	50
Protein concentrates (commercial preparations)*	50–70
Protein hydrolysates (commercial preparations)*	65–75
Casein (crude edible variety)	85

* Many types available concentration varies widely

It is often difficult to persuade a sick patient to eat the requisite amount of food Anorexia unpalatability of the diet or loss by vomiting or diarrhea are factors contributing to this difficulty Encouragement by the nursing attendants is of great importance if success is to be attained

A diet which contains 155 Gm of protein (Table 41) may be used satisfactorily in patients who have only a moderate deficiency and who are not seriously ill It is often necessary however to give smaller quantities of food and a larger percentage of the protein in the form of concentrates some of which are listed in Table 42 Concentrates can be incorporated in milk

amined for amino acid and electrolyte content If nutrition is supplied only by the parenteral route all the essential amino acids must be included in adequate amounts and perhaps other amino acids as well with sufficient sodium chloride potassium calcium etc to meet bodily needs In patients with edema the salt content should be low Vitamins should be added to the amino acid glucose mixture or given intramuscularly in daily amounts approximately as follows thiamine 5–10 mg riboflavin 5–10 mg niacinamide 50–100 mg ascorbic acid 100–300 mg

Acute Protein Deficiency The treatment of acute protein deficiency syndromes, in the presence of surgical shock includes transfusion of blood plasma albumin or a combination of all three substances If hemorrhage is the cause of the deficiency whole blood is indicated The quantity of blood or plasma to be given must be carefully judged by both clinical appraisal and laboratory tests The circulation may be considered adequate *if the urine output is* normal and the specific gravity ranges from 1 010 to 1 025 Hematocrit determinations are also useful in determining the amount of therapy needed There is real danger of giving too large an amount of fluid too rapidly with resultant pulmonary edema After shock has been combated oral feeding should be instituted as soon as possible

Concentrated Human Plasma and Albumin At times in chronic protein deficiency concentrated human plasma or human albumin solutions may be employed advantageously Both have the disadvantages of high salt content deficiency in the amino acids isoleucine and tryptophan and high cost The virus of infectious hepatitis may be transmitted by plasma transfusions and cause a serious complication In addition sensitivity reactions may occur Furthermore the use of plasma entails the administration of fairly large amounts of fluid

A salt poor human albumin fortified with isoleucine and tryptophan has been found by Thorn and co workers to have a diuretic action in the nephrotic syndrome and in cirrhosis of the liver It may be useful in amounts of 50 Gm daily and is given in 10 per cent concentration in 5 per cent glucose at a rate of 100 cc per hour If administered between lunch and supper or after the night meal it will not interfere with the patient s intake of food Nitrogen balance may be maintained by administering human albumin solutions as the sole source of protein Both plasma and albumin are utilized by the body for protein regeneration but more slowly than protein hydrolysates Amino acids may be beneficial in conjunction with intact blood proteins by sustaining liver function or by maintaining a more vigorous turnover of nitrogen

Individual Amino Acids The influence of individual amino acids in human nutrition is the subject of particular study at present Methionine has been used in the treatment of disease of the liver, particularly cirrhosis and appears to be of value Tryptophan has been shown to be intimately related to niacin metabolism and will be discussed subsequently in the section on vitamins

The rehabilitation of patients with severe protein deficiency may take long periods of time and in conditions associated *with continuous loss of protein* from the body may be impossible The slow recovery may be appreciated in view of the considerations already discussed

When hypoproteinemia occurs in association with heart failure the salt and fluid intake must be carefully regulated *when it accompanies azotemia* the problem is extremely difficult and treatment must be directed toward the most urgent needs

LOW PROTEIN DIETS

Diets low in protein are *indicated in* acute and subacute nephritis and in azo-

and controversy There is considerable evidence to indicate that whole protein is superior to protein digests Indications for the *oral* use of hydrolyzed protein are few Such therapy may be of benefit when digestive secretions are defective as in chronic pancreatitis following resection of the head of the pancreas in ileitis or ulcerative colitis and in conditions in which portions of the intestinal tract have been removed or short circuited Oral hydrolysates may also be of value in the treatment of certain allergic states Many of the protein hydrolysates have an objectional taste although palatable preparations have recently become available such as melactin or protinal

TABLE 44 TUBE FEEDING FORMULA
(80 Grams Protein 1500 Calories)

Eggs 4
Evaporated milk 1½ cups
Breakfast cream cup
Karo dark ½ cup
Brewer's yeast 2 tablespoons
Casec 20 grams or 3 tablespoons
Water 1 cup

The above ingredients make approximately 000 cc (one quart) of formula

Most patients will tolerate 100–200 cc administered at hourly intervals

Orange juice (¼ cup) should be given with one morning and one afternoon feeding

Salt may be added as indicated (5 10 Gm daily)

Pectin apple powder or apple sauce may be used to prevent diarrhea (3 tbs powder or 50 Gm apple sauce)

Indications for the intravenous administration of protein hydrolysates include conditions which interfere with the ingestion digestion and absorption of food and those in which complete rest of the gastrointestinal tract is essential In the absence of excessive loss of nitrogen from the body it is possible to maintain nitrogen balance with the parenteral administration of amino acids or hydrolyzed protein It is difficult to alter the nitrogen deficit in post traumatic and postsurgical convalescence and routine use of hydrolysates in these conditions is certainly not advisable However in persons in whom protein depletion was present prior to injury or operation or in whom complications occur such therapy should be instituted

The *quantity* of hydrolyzed protein which may be given intravenously is limited since a concentration above 5 per cent is not well tolerated The polypeptide content of the hydrolysate appears to limit tolerance as it has been shown that mixtures of pure amino acids may be given in 8 per cent concentrations without ill effect There is some evidence that certain peptides may be needed for the maintenance of normal nutrition Mixtures of amino acids or protein hydrolysates are usually administered in 5 per cent glucose at a rate of 200–500 cc per hour If the rate is too rapid nausea vomiting and diarrhea may occur These or other reactions such as chills fever venous thrombosis and allergic manifestations have been noted in 5 to 10 per cent of patients Cardiac or renal disease may decrease tolerance to intravenous feeding

The amount of protein which may be supplied by vein is 100–150 Gm per day of which not over 50 Gm should be given at one time The administration of 150 Gm of protein requires 3000 cc of fluid and if given in 5 per cent glucose will furnish 1200 calories Even this low caloric intake may assist in minimizing the metabolic loss of protein As much as 225 Gm of protein hydrolysate has been given in twenty four hours but the time required for such infusions seriously interferes with the patient's rest and comfort. Butler and Talbot suggested adding 300 cc of 50 per cent glucose to 1 liter of 5 per cent protein hydrolysate in 5 per cent glucose to provide additional calories The amount of glucose administered should not exceed 0 8 Gm per kg body weight per hour to avoid glycosuria and diuresis

The hydrolysates used should be ex

the liver and muscles in the form of glycogen and is present in the blood and extracellular fluids as glucose

Carbohydrate is indispensable for the function of both the heart and the nervous system Hypoglycemia may precipitate angina pectoris severe myocardial injury, and even death in older individuals with arteriosclerosis Permanent brain damage may follow prolonged hypoglycemic episodes

Carbohydrate has an important protective and detoxifying action in the liver Acetyl groups derived from carbohydrate function in acetylation of a number of compounds including sulfonamide drugs glycuronic acid derived from carbohydrate, combines with compounds containing phenolic hydroxyl groups This mechanism is probably of assistance in the regulation of steroid hormone metabolism and in the protection of the body from excessive accumulation of the sex hormones

Carbohydrate has a protein sparing action by decreasing the rate of deamination of amino acids in the liver It also has *an antiketogenic action* by *inhibiting the* breakdown of fatty acids in the liver

Glycogen stores in the liver are highest when the diet contains large amounts of carbohydrate intermediate when the diet is high in protein and lowest when the diet is high in fat A high carbohydrate diet is desirable for protection of the liver from injury by insuring adequate storage of glycogen Insulin should not be given in conjunction with intravenous glucose or high carbohydrate diets to normal individuals Instead of improving liver glycogen stores more carbohydrate is withdrawn to the muscles and less glycogen is deposited in the liver

Carbohydrate and Vitamin B Complex Vitamins of the B complex in *particular* thiamine niacin and riboflavin have been shown to function as co enzymes in the breakdown of carbohydrate If a single factor is missing metabolism cannot proceed normally In the presence of thiamine deficiency, one of the intermediate metabolites in the breakdown of glucose, pyruvic acid accumulates in the blood and tissues The glucose tolerance test in advanced thiamine deficiency resembles that obtained in diabetes mellitus *

In some types of chronic deficiency of the vitamin B complex changes occur in the intestinal mucous membrane or in enzyme systems which interfere with the absorption of glucose and of other factors from the intestine In these conditions a flat glucose tolerance test is observed

It is obvious that diets high in carbohydrate necessitate an ample supply of the entire vitamin B complex If sugar and highly milled cereals account for a large percentage of the diet, vitamin B complex deficiency may develop The enrichment program in which the B vitamins are added to refined cereals in amounts equivalent to whole grain products is an attempt to provide an adequate intake of these factors for population groups who use such cereals *as the staple articles of diet*

DISTURBANCES OF CARBOHYDRATE METABOLISM OTHER THAN DIABETES MELLITUS

In certain diseases impairment of digestion and absorption of carbohydrate result in hyperglycemia In the *steatorrheas* (sprue and the celiac syndrome) absorption of glucose is impaired and excessive fermentation in the intestinal tract leads to gaseous distention The glucose tolerance test has a flat curve due to poor absorption while the intravenous glucose tolerance test is normal It has been shown that patients with steatorrhea can utilize two particular carbohydrate-containing foods *better than others—strawberries* and bananas The explanation for this is unknown but is probably related to the mechanism

* See also Chapter 48

TABLE 45 LOW PROTEIN DIET
(*45 Grams Protein * 1900 Calories*)

Milk	2 cups
Cream	½ cup
Meat	1 small serving 1½ oz
Potato	2 servings ½ cup each
Vegetable	3 servings ½ cup each
Fruit	1 serving ½ cup
Fruit juice	2 cups (one citrus and one other)
Bread†	2 slices
Cereal†	1 serving ½ cup
Butter or fortified margarine	2 tbs
Mayonnaise or salad dressing	1 tbs
Jam or jelly	1–2 tbs
Sugar	1–2 tbs

SUGGESTED MEAL PLAN

Breakfast	*Noon*	*Night*
Fruit juice 1 cup	Vegetable ½ cup	Meat 1 serving
Cereal ½ cup	Salad ½ cup	Potato 1 cup
Cream ½ cup	Mayonnaise 1 tbs	Vegetable ½ cup
Toast 1 slice	Bread 1 slice	Butter 2 tsp
Butter 2 tsp	Butter 2 tsp	Fruit juice 1 cup
Jelly 2 tbs	Fruit ½ cup	Sugar 2 tsp
Sugar 1 tbs	Milk 1 cup	
Milk 1 cup		

Coffee or tea as desired

* If less than 45 Gm of protein is included in the diet vitamins of the B complex should be administered as supplements.
† Enriched or whole grain

temia unassociated with marked loss of protein from the body Restriction of protein decreases the work of the kidney in these conditions and favors restoration of function If such a regimen is to be carried out for more than a few days sufficient protein for maintenance needs should be supplied—about 0 6 Gm per kg body weight per day Excessively low protein diets if continued for long periods of time will result in protein deficiency A low protein diet is given in Table 45

Carbohydrates

CARBOHYDRATES furnish between 50 and 60 per cent of the total caloric intake in the average American diet In the digestive processes carbohydrates are broken down to monosaccharides which are absorbed either by diffusion or by a specific mechanism which probably involves phosphorylation Absorption is influenced by the food mixture in the intestine the state of the intestinal mucous membrane the function of certain endocrine glands—particularly the anterior pituitary, thyroid and adrenal cortex—and by the intake of vitamins especially of the B complex

Carbohydrate is utilized by the body chiefly as a source of energy and is more efficient than protein or fat in providing energy for muscular exercise A certain amount of carbohydrate is indispensable since the blood sugar concentration must be maintained above a critical level or serious damage will result If the diet fails to supply adequate carbohydrate it is formed from protein or fat Carbohydrate is

that unsplit fat can enter the lacteals directly while fatty acids pass into the portal vein and are carried immediately to the liver

In obstructive jaundice the absorption of fat is seriously impaired but the splitting to fatty acids and glycerol is not affected This illustrates the importance of bile in the absorptive process In the steatorrhea of sprue fat is also broken down into fatty acids which again are not absorbed The poor absorption cannot be explained by a decrease in available bile It has been postulated that there may be a defect of the phosphorylating mechanism which in turn is due to a deficiency of some member of the vitamin B complex Folic acid is one of the possible factors involved

In the liver fatty acids are incorporated into choline containing phospholipids and transported in this form to various parts of the body In the absence of choline, or of a supply of labile methyl groups for the formation of choline fat accumulates in the liver When fat reaches some depot in the body it does not remain inert a constant interchange between dietary and depot fatty acids takes place

The liver is responsible for degradation *of fatty acids into four carbon fragments or* ketone bodies These are carried to the tissues where they are oxidized to carbon *dioxide and water with the* liberation of energy This utilization occurs chiefly in *the muscles and kidneys and when the* maximum rate is exceeded ketonemia and ketonuria occur A discussion of the acidosis which occurs when excessive ketone bodies are formed will be found in Chapter 31

DISEASES REQUIRING REGULATION OF FAT INTAKE

An excessive intake of fat (and calories) will lead to obesity and hence is to be avoided The fat content of the diet should be low in obstructive jaundice and in other steatorrheas such as sprue or the celiac syndrome due to *impairment of fat absorp*tion In rare instances pancreatic deficiency may be so profound that both digestion and absorption of fat are impaired The severe diarrhea which occurs responds poorly even to restriction of fat intake In disease of the liver, dietary fat should be limited in amount and lipotropic material supplied in the form of choline and/or methionine together with an abundance of good protein In starvation fats should be administered cautiously as they lead to serious gastrointestinal upsets which may influence prognosis unfavorably

The importance of diets low in fat and cholesterol in the prevention or treatment of arteriosclerosis remains a debatable question * It would seem advisable to avoid diets high in fat in arteriosclerotic diseases but until more definite information is available rigid limitation of fat or cholesterol intake seems unwarranted

A low fat diet which may be useful in some of the above conditions is given in *Table 46*

Persons with gallbladder disease should probably avoid foods containing large *amounts of cholesterol which* may be incorporated in gallstones Fats particularly cooked fats are usually not well tolerated in the presence of pathology of the gall bladder However it has been noted frequently *that olive oil cream* and butter may be taken without difficulty and these have been prescribed in certain regimens to stimulate contraction of the gallbladder

In the treatment of essential hypercholesteremia cholesterol intake can be restricted by administering an all vegetable diet since plant sterols are not absorbed from the intestinal tract Such treatment is not always effective since cholesterol is formed endogenously from acetate

Recently fat emulsions suitable for intra

* See also Chapter 11

of absorption These foods, with a high protein and low fat diet are helpful in the treatment of steatorrhea The administration of folic acid leads to better absorption of glucose in the steatorrheas and in certain other syndromes of vitamin B complex deficiency including nutritional macrocytic anemia

Hypothyroidism is associated with a decrease in absorption of carbohydrate from the intestinal tract in hyperthyroidism the rate of absorption is increased Hypofunction of the anterior pituitary as in Simmond s disease, likewise is associated with poor absorption of carbohydrates—probably as a result of secondary hypothyroidism The administration of thyroid preparations will alleviate this condition In Addison s disease poor absorption of carbohydrate is due to the decrease in sodium and chloride in the blood Administration of salt or of adrenal cortical hormones corrects this abnormality *

* See also Chapter 30

Functional hypoglycemia of mild degree is probably more common than any of the types of hypoglycemia noted above Symptoms occur several hours after a meal particularly one high in sugar The mechanism by which an excessive fall in blood sugar is produced may be the same as that noted in diseases of the pituitary or adrenal gland In these conditions the liver apparently fails to respond with an increase in the output of glucose until the blood sugar has fallen to a lower level than normal Treatment consists in restricting free sugar in the diet and substituting more slowly absorbed carbohydrate, such as starchy vegetables and cereals A high protein diet is also of assistance in functional hypoglycemia since there is apparently no decrease in the ability of the liver to manufacture glucose from amino acids

Further discussion of abnormalities of carbohydrate metabolism of diabetes mellitus and hyperinsulinism will be found in Chapter 31

Fats in Nutrition

FAT is used in the body largely as a source of energy and as a constituent of tissues It also serves as a carrier of certain vitamins

Cholesterol which occurs in close association with fat is a member of a group of steroid compounds which include the bile acids and the sex and adrenal cortical hormones Cholesterol esters are normally found chiefly in the blood and in the adrenal cortex They also occur as deposits in the blood vessels in liver cells and in gallstones Recent studies suggest that diets high in fat and cholesterol may play a role in the pathogenesis of arteriosclerosis * Elevated blood cholesterol levels are found in hypothyroidism in the nephroses and were common in diabetes mellitus prior to the discovery of insulin Low levels occur in hyperthyroidism and in certain infections A condition known as essential hypercholesteremia is also occasionally encountered

* See also Chapter 11

The digestion and absorption of fat is largely dependent on the action of pancreatic lipase and bile salt It is believed that absorption occurs by the combination of water insoluble fatty acids and water soluble bile acids for passage through the intestinal wall In the intestinal mucosa fat (triglyceride) is resynthesized by a process which probably involves phosphorylation The major portion of fat then enters the lymphatic system Frazer has suggested

taken in hot climates as much as 20–30 Gm of salt may be ingested daily The salt content of sweat, in an unacclimatized person, may be as high as 2–3 Gm per L, while after acclimatization it drops to about 0 5 Gm per L This change decreases the need for extra salt in the diet

The minimum requirement of sodium and chlorine is low balance can be maintained on an intake of approximately 1 Gm daily The amount of salt excreted by the kidney is dependent on the amount ingested in the absence of significant sweating When the diet is low in salt, almost no sodium or chlorine is excreted in the urine The efficient mechanism which regulates reabsorption by the renal tubules is controlled in part by hormones of the adrenal cortex In Addison s disease large amounts of sodium chloride are lost in the urine, and salt depletion is responsible for many features of this condition * When it is necessary to administer extra salt it may be given in a concentration of 0 1 per cent in drinking water or in the form of compressed 0 5 Gm tablets to be taken with a cup of water

The normal level of sodium in the blood is 140 mEq per L that of chloride 104 mEq per L

Low Salt Diets Because of the importance of sodium in the pathogenesis of edema diets low in salt are prescribed in most of the diseases in which edema is a prominent feature such as acute hemorrhagic nephritis, the nephrotic syndrome, congestive heart failure hypoproteinemia and cirrhosis of the liver Low salt diets have also been used recently in the treatment of hypertension Kempner reported that a diet of rice and fruit led to clinical improvement in a number of patients with hypertension Whether or not the low salt content of the rice diet is the entire explanation of the beneficial effects noted has not been conclusively settled However, similar improvement has been observed with more acceptable and adequate diets low in salt The place of these diets in the therapy of hypertension is not finally evaluated but further trial is warranted *

Foods of plant origin such as nuts, fruits cereals, and legumes are low in salt, while foods of animal origin are relatively high in sodium and chlorine Table 47 gives a diet containing approximately 0 25 Gm of sodium, such as has been prescribed in the therapy of hypertension Less severe restriction is usual in the control of edematous states Suggestions regarding this are included in the table

Salt depletion may occur if low sodium diets are prescribed for long periods of time Careful search for manifestations of this syndrome, such as lassitude, nausea weakness peripheral vascular collapse and muscle cramps should be part of the routine management of patients on low salt regimens As a check on the salt intake, the test proposed by Fantus may be used as a rough estimate of the quantitative excretion of chloride †

POTASSIUM

The minimal daily requirement of potassium is similar to that of sodium The kidney maintains a balance between the intake and output in a manner resembling that for sodium, except during fasting and whenever there is damage or death of tissues which allows escape of intracellular potassium when this ion is excreted in the urine Persistence of such losses if large may lead to potassium deficiency The concentration of potassium in the serum is much lower than that of sodium 3 5 5 mEq per L

IODINE‡

The daily requirement for iodine is small about 0 15–0 30 mg for an adult (0 002–

* See also Chapter 30

* See also Chapter 15

† See Chapter 48

‡ See also Chapter 29

TABLE 46 LOW-FAT DIET*
(35 Grams Fat, 1950 Calories)

Milk, skim	3½ cups
Meat or fish, very lean	1 serving, 5 oz or 2 small servings, 2½ oz
Potato	1 serving, ½ cup
Vegetable	4 servings, ½ cup each (1 green or yellow and one raw)
Fruit	2 servings, ½ cup each (one citrus and one other)
Bread†	6 slices
Cereal†	1 serving, ½ cup
Butter or fortified margarine	3 level tsp
Jelly	1 tbs
Sugar	2 tbs

SUGGESTED MEAL PLAN

Breakfast	*Noon*	*Night*
Citrus fruit juice, 1 cup	Soup, 1 cup—use ½ cup puréed vegetable and ½ cup skim milk	Meat, 5 oz
Cereal, 1 serving	Salad, 1 serving	Potato, 1 cup
Bread, 2 slices	Bread, 2 slices	Vegetable, ½ cup
Butter, 1 level tsp	Butter, 1 level tsp	Bread, 2 slices
Milk, skim, 1 cup	Milk, skim, 1 cup	Butter, 1 level tsp
Jelly, 1 tbs	Fruit, ½ cup	Milk, skim, 1 cup
Sugar, 2 tbs		

Do not use Fried or greasy food, pork, ham sausage, salt meat, glandular meats, gravies sauces, broth, spices, salad dressings

* This diet is relatively low in cholesterol from animal sources (150–200 mg)
† Enriched or whole grain

venous administration have been prepared by means of high pressure homogenization and proper stabilizing agents Such emulsions may prove valuable in furnishing adequate calories in a small amount of fluid to the patient who must receive all nutrients by the parenteral route One liter of a 15 per cent emulsion will furnish about 1500 calories The only untoward effects of administration of these emulsions have been febrile reactions and gastrointestinal disturbances but further investigation is needed before recommending these preparations for general use

Minerals in Nutrition

AT LEAST thirteen mineral elements are required by the body calcium magnesium, sodium potassium, phosphorus sulfur and chlorine (principal mineral elements) and iron, copper, iodine, manganese, cobalt and zinc (trace elements)

Minerals are found widely distributed ... foods and for many of them there is ... tle danger of deficiency occurring Dis... ssion will be limited to those minerals ... ich are of importance in clinical medi...

WATER AND ELECTROLYTES

Problems of water and electrolyte balance are discussed in Chapter 19 and only a few remarks concerning electrolytes will be included here

SODIUM CHLORIDE

In an average adult diet the usual intake of sodium chloride ranges from 8 to 15 Gm daily Five grams may be considered a liberal allowance except for persons who sweat profusely When heavy work is under-

0 004 mg per Kg of body weight) This requirement may be satisfied by the use of iodized salt Iodine is essential for the *formation of the thyroid hormone*, and when the intake is deficient so called endemic goitre develops It is particularly important that the need for iodine is met in the adolescent period and during pregnancy

IRON

Iron is necessary for the formation of hemoglobin and is a constituent of cellular enzymes such as catalase cytochrome and peroxidase The excretion of iron is negligible and the amount present in the body is controlled by selective absorption from the intestinal tract A large percentage of iron in the body is present in the red cells as hemoglobin It is also stored in the liver spleen and bone marrow and is found in muscle hemoglobin and iron-containing enzymes

When the reserve stores of iron in the body are depleted iron absorption is increased many times above normal but is still somewhat inefficient amounting to only a small percentage of a given dose Therapy must accordingly be prolonged for many weeks after severe hemorrhage The presence of infection has been shown to interfere with the absorption and utilization of iron

Iron Deficiency Anemia* Anemia due solely to dietary deficiency of iron is uncommon except during the periods of increased need such as growth pregnancy and lactation The most common cause of iron deficiency anemia is acute or chronic loss of blood It has been suggested that 12 mg of iron is an adequate daily allowance for adults 15 mg for women during pregnancy and lactation The normal adult male needs relatively little iron The infant at birth has a certain amount of stored iron the quantity being related to the maternal supply during pregnancy

Measurement of the level of serum iron is of assistance in detecting iron deficiency anemia The normal concentration varies from 80 to 200 μg per 100 cc of blood while in iron deficiency a concentration of less than 50 μg is obtained Iron deficiency anemia is hypochromic the cells being either small or normal in size The color index and mean corpuscular hemoglobin concentration are low

For the prevention of iron deficiency anemia during pregnancy and lactation and to ensure adequate fetal stores it seems advisable to administer some form of iron such as ferrous sulfate 0 3 Gm *three times daily to all pregnant women* In the treatment of iron deficiency anemia 0 3–0 6 Gm of ferrous sulfate may be administered three times a day after meals Other forms of iron are equally satisfactory if given in sufficient amounts

Iron often causes gastrointestinal disturbances such as indigestion pain diarrhea nausea or vomiting If one preparation causes distress it usually is possible to find another which can be tolerated The use of intravenous iron is seldom indicated Due to the inability of the body to excrete iron in significant amounts the repeated intravenous administration of this mineral may lead to deposition of excessive stores in the liver and other organs

Foods which are good sources of iron include the parenchymatous organs lean meats leafy vegetables dried peas and beans whole grain or enriched cereals oysters eggs dates figs prunes raisins and dried peaches

COPPER

Adults require approximately 1–2 mg of copper daily infants and children 0 05 mg per Kg body weight These quantities are practically always supplied by a good diet There is little evidence that the administration of copper is of assistance in the therapy of iron deficiency anemias

* See also Chapter 14

TABLE 47 LOW SALT DIET

45 Grams Protein 600 Calories 250 Milligrams Sodium (Approx.)

BREAKFAST

Fruit	orange ½ grapefruit or 1 tangerine
Bread or cereal	1 slice low salt bread and ⅔ cup oatmeal wheatena cream of wheat or farina or c p puffed wheat or puffed rice
Milk	⅔ cup
Egg	1 hard cooked soft cooked or poached
Salt poor butter or margarine*	2 tsp
Sugar	2 tbs
Tea or black coffee	As desired

DINNER AND SUPPER

Meat fish or chicken	piece the size of a thin chop (3″×2½″×½″) Use only lean beef veal white meat of chicken breast of duck pork liver or rabbit Catfish halibut or cod may be used in place of meat The meat or fish may be fresh or frozen
Vegetables	cup from the list below
Fruit and fruit juice	1 serving each from the lists below
Low salt bread	slice
Salt poor butter or margarine*	2 tsp

Vegetable list (Fresh or frozen only)		*Fruit juice list* (½ Cup Unsweetened)	*Fruit list* (Fresh only)
Asparagus	Okra	Apple juice	Apple 1
Green beans	Onions	Grapefruit juice	Banana 1
Brussel sprouts	Parsnips	Grape juice	Figs 3
Broccoli	Peas (fresh only)	Lemonade	Grapefruit ½
Cabbage	Pumpkin	Orange juice	Grapes ½ cup
Cucumbers	Radishes	Pineapple juice	Mandarine 1
Chicory	Squash		Orange 1
Eggplant	Tomatoes		Peach 1
Green peppers	Turnip greens		Pear
Lettuce			Plums 4

FOLLOWING CONDIMENTS MAY BE USED

Allspice	Lemon juice	Pepper red
Caraway	Mustard powder (not prepared mustard)	Pepper white
Cinnamon	Nutmeg	Sage
Garlic	Paprika	Thyme
Ginger	Pepper black	Tumeric
Lemon extract		Vanilla extract
		Distilled vinegar

Low salt bread contains about 2 mg sodium per 100 Gm (4 slices) A recipe for 2 loaves is as follows flour 2 cups shortening 1 tbs sugar 1 tbs moist yeast 2 tbs water 2½ cups

RULES FOR FOLLOWING DIET

1 Do not fry anything meat must be boiled roasted or broiled
2 Cook vegetables in plain water† for only 10–25 minutes the butter allowed in the diet may be used on the vegetables
3 Do not eat ham bacon salt pork sausages corned beef luncheon meats canned meats cheese olives pickles salad dressings canned vegetables and soups soda crackers
4 Do not use any salt in cooking or add salt at the table
5 Do not eat foods prepared with baking soda or baking powder
6 You may use lemon juice on salads

* The sodium content of margarine may be greatly reduced by melting skimming off the surface foam and pouring off the clear part [illegible]

ciated with defects in the *coagulation of* blood is seldom indicated

PHOSPHORUS

The daily allowance of phosphorus in the diet should be at least equal to that of calcium for children and for women during pregnancy while other adults should receive about one and a half times as much phosphorus as calcium If the calcium and protein needs of the body are supplied *by common foods the phosphorus require* ment will also be satisfied in most instances

Phosphorus has many important functions in the body It is used in the construc*tion of nervous and muscle* tissue, and in the formation of skeletal structure in conjunction with calcium and vitamin D It is essential in the metabolism of fats and carbohydrates participates in regulation of hydrogen ion concentration and is active in many phases of metabolism as a constituent of enzymes and of compounds important in the release of energy

When the diet is inadequate or unbalanced with respect to calcium and phosphorus in *childhood skeletal growth is* poor and rickets may appear while in adults osteoporosis fragile bones and osteomalacia may occur

FLUORINE

While it is uncertain that fluorine is a human dietary essential interesting relationships between fluorine and certain abnormalities of the teeth have been discovered The ingestion of an excessive amount of fluorine during tooth development through the use of drinking water containing more than 2 5 parts per million causes mottling of the enamel of the teeth. When fluorine is present in the water in *greater than one part per million the in*cidence of dental caries is low in children who have received this water during the period of tooth development When the *drinking water contains minimal amounts* of fluorine, a high incidence of dental caries has been observed

Fluoridation of public water supplies has been initiated in many communities and appears to be a valuable measure in the mass prevention of dental caries No harmful effects have resulted from fluoridation when the recommended concentration of approximately 1 part per million is maintained Since fluoridation is most effective *during the years of enamel calcification* topical application of fluoride is advisable for children whose teeth are already calcified when fluoridation is started

Vitamins

THERAPY with vitamins has been widely and often indiscriminately used There are certain specific indications for such therapy others which are less clear cut To use any vitamin rationally and wisely it is essential *to understand its function in* the body and to appreciate the circumstances under which deficiency may occur Many of the vitamins are known to be active fractions of enzymes which are *essential in metabolic* processes of all of the cells of the body It follows that the first evidence of vitamin deficiency is a biochemical or functional change while structural lesions demonstrable clinically are late in appearance The early diagnosis of vitamin deficiency is accordingly difficult The first clinical signs and symptoms are nonspecific and while laboratory tests may be of great assistance few are available to the general prac*titioner*

In this country, vitamin deficiency due

COBALT

Cobalt has been shown to be a constituent of Vitamin B_{12} which is the antipernicious anemia factor of liver This vitamin is an essential nutrient for man and many animal species *Cobaltous chloride has been* used recently in an attempt to influence the refractory anemias associated with such conditions as chronic infection or neoplasia Results have been equivocal and further studies of the toxicity of cobalt should be undertaken before this form of therapy can be recommended

CALCIUM

Calcium has a number of important functions in the body, among the most important of which are its role in the formation of bones and teeth in the blood clotting mechanism and in neuromuscular excitability The utilization of calcium is influenced by a number of factors Vitamin D and ascorbic acid must be adequately supplied and the quantities of phosphorus and fat in the diet affect the completeness of calcium utilization Diets high in protein may increase the absorption of calcium The interrelationships of calcium phosphorus vitamin D and the parathyroid glands are mentioned subsequently in the discussion of Vitamin D metabolism

The recommended allowance of calcium is 1 Gm daily for adults 1 4 Gm during the *period of rapid growth in adolescence 1 5* Gm in pregnancy and 2 Gm during lactation The most important calcium rich food is milk one quart furnishing 1 15 Gm of calcium Other foods high in calcium are egg yolk molasses clams certain greens (collard mustard and turnip) figs filberts and almonds *Much of the calcium in* vegetables may be unavailable due to the formation of insoluble calcium oxalate If milk is not included in the diet the calcium intake may be low

Calcium Deficiency

Calcium deficiency is manifested by tetany, with characteristic carpopedal spasm *and at times convulsive seizures* Laryngospasm may also occur, particularly in children Trousseau s and Chvostek s signs are positive and the concentration of blood calcium falls to low levels, usually less than *8 mg per 100 cc, compared* to the normal level of 9–11 mg Tetany is a common accompaniment of rickets and osteomalacia It also occurs in sprue, the celiac syndrome, and other steatorrheas due to the combination of calcium with fatty acids to form insoluble soaps

Treatment Immediate treatment of acute tetany with spastic or convulsive phenomena, is the intravenous administration of calcium This is best given in the form of calcium gluconate, 10–30 cc of a *10 per cent solution Subsequent treatment* includes the institution of a diet high in calcium particularly in milk which furnishes both calcium and phosphorus and the daily administration of 10 000 International Units or more of vitamin D Calcium may also be administered orally in the form of the lactate 2 Gm, or gluconate, 4 Gm to be taken in a glass of water three or four times daily between meals

Hypocalcemia and tetany also occur in hypoparathyroidism In this condition the *serum phosphorus level is normal or high* and the dietary intake of phosphorus should be limited to 0 5–0 6 Gm daily Accordingly milk should not be used as a source of extra calcium Treatment includes *the administration of parathormone or* preferably dihydrotachysterol in addition to calcium

Administration of calcium has been sug [illegible]

marked osteoporosis The value of calcium in these conditions has not been proved

Although calcium is important in the *blood clotting mechanism it is rarely if* ever a limiting factor in coagulation Administration of calcium in diseases asso-

carrots, squash, sweet potatoes and yellow fruits such as apricots and cantaloupe

Vitamin A may be administered in the form of cod liver oil halibut liver oil percomorph oil or concentrates Two tea spoonfuls of cod liver oil (U S P) will supply about 7000 International Units of vitamin A Capsules containing 10 000 25 000 and 50 000 International Units of vitamin A are available The therapeutic dose of vitamin A should be 10 000–25 000 International Units two to four times daily When abnormality of fat absorption is present vitamin A should be given as an aqueous preparation of which several are available

In hypothyroidism diabetes mellitus and liver disease therapy with vitamin A rather than carotene is essential since there is difficulty in conversion of carotene to vitamin A Vitamin A can be given par enterally if oral administration is contra indicated

Night blindness responds rapidly to treatment improvement being noted within a few hours Lesions of the skin and mucous membranes respond slowly and many months of therapy may be needed for restoration to normal

There are few untoward reactions to the administration of vitamin A in the usual therapeutic amounts Allergy to fish liver oil is occasionally observed Toxicity has been noted in children who received enor mous quantities of vitamin A approximat ing 250 000 International Units daily for months Manifestations included hepato megaly, splenomegaly hypoplastic anemia clubbing of the fingers and sparse coarse hair Most of the findings disappeared after therapy was discontinued In adults the use of 100 000 International Units daily for thirty six months was reported to produce an increase in the concentration of choles terol phospholipids and vitamin E in the ed

VITAMIN B COMPLEX

The vitamin B complex consists of a number of factors of which eleven are available in pure form Not all of these vitamins have been shown to be essential in human nutrition Thiamine, riboflavin niacin pyridoxine and pantothenic acid are components of one or more enzymes which are of vital importance in inter mediary metabolism Two B vitamins choline and inositol have lipotropic activ ity while two have antianemic properties folic acid and vitamin B_{12}

Vitamin B Complex Deficiency

Deficiency of vitamins of the B complex is one of the most frequently encountered syndromes of malnutrition Since many of the B complex vitamins are closely associ ated in their distribution in nature d ficiency of several factors is much mo common than that of a single vitamin

The precipitating and contribut causes of vitamin B complex deficiency numerous Diseases associated with an crease in metabolism such as febrile nesses hyperthyroidism and leukemia to deficiency by increasing requiren High carbohydrate diets and the u intravenous glucose as the sole metho feeding increase the requirement of vitamins because of their role i metabolism of carbohydrate Fol severe injuries there also appears increased need for these factors

Malabsorption occurs in diarrh cases inflammatory lesions of the i tract and in congestive heart fai ficiency of this group of vitamins poor absorption from the intesti as evidenced by flat glucose toler and changes in the roentgenogr ture hypersegmentation and p barium with loss of the norm bone pattern

Symptoms of vitamin B co ciency have been reported to be

solely to an inadequate diet is less common than is deficiency secondary to some pathologic state which influences the utilization or increases the requirement of nutrients Thus, evidence of deficiency should be suspected and carefully searched for in hypermetabolic states in conditions involving disturbances of ingestion, digestion or absorption of food in disease of the liver and in other diseases which influence the utilization destruction, or excretion of nutrients

VITAMIN A

Vitamin A, one of the fat soluble vitamins is absorbed from the intestinal tract with the aid of bile salts and is stored in the liver Almost no vitamin A is excreted Vitamin A is taken into the body in two forms—as vitamin A itself and as the provitamin carotene Carotene accounts for more than half of the dietary supply of vitamin A and is less well utilized than the preformed vitamin The recommended daily intake of vitamin A is 5000 International Units Vitamin A functions in the body in two ways in the maintenance of normal epithelium and in the regeneration of rhodopsin in the retina

Measurement of the level of carotene in the blood is of assistance in determining the recent dietary intake of this substance while determination of vitamin A concentration in the blood gives information of bodily stores of this factor Normal values for carotene in the blood are 50–150 μg per 100 cc, for vitamin A 30–90 μg for 100 cc

Vitamin A Deficiency

The signs of vitamin A deficiency are dryness and scaling of the skin (xerosis) with keratinization of the hair follicles (follicular hyperkeratosis) and night blindness Skin lesions appear first on the anterolateral surfaces of the thighs and extensor aspects of the arms and later may become general in distribution, usually sparing the face The early lesions have the appearance of permanent goose flesh Similar keratinizing metaplasia involves the mucous membranes particularly the conjunctivae There is dryness of the eyes or xerophthalmia and in late stages infection may occur with destruction of the cornea, panophthalmitis and loss of vision Thickening of the conjunctivae has been considered a manifestation of vitamin A deficiency by some observers, but there is not adequate experimental support for this belief Abnormalities of dark adaptation have been shown to be the earliest findings in experimentally induced vitamin A deficiency

The concentration of vitamin A in the blood is decreased in many infections and returns to normal following recovery, without therapy having been administered. A reduction in blood vitamin A values also occurs in disease of the liver

Vitamin A deficiency is often observed in conditions in which bile is absent from the intestinal tract in steatorrhea such as sprue celiac disease and pancreatic fibrosis, and in cirrhosis of the liver It may also occur in chronic inflammatory disease of the small intestine, after short-circuiting operations, and following the promiscuous administration of mineral oil which interferes with the absorption of carotene and to a less extent of vitamin A In diabetes mellitus and in hypothyroidism there may be defective conversion of carotene to vitamin A with resultant signs of both hypercarotinemia and vitamin A deficiency

Treatment. The treatment of vitamin A deficiency consists of the institution of a diet high in vitamin A–containing foods and the administration of concentrates of vitamin A The richest food sources of vitamin A are liver, cream butter, cheese, and egg yolk, good sources of carotene are green leafy and yellow vegetables such as turnips, mustard, and beet greens, spinach,

rapidly following the administration of thiamine

Several other syndromes have been reported which seem to be related to thiamine deficiency During World War II, a type of optic or retrobulbar neuritis at times associated with paralysis of the extra ocular muscles occurred in certain concentration camps and appeared to be due in part at least to thiamine deficiency Early treatment stopped the progress of the disease and led to some improvement Wernicke's encephalopathy characterized by *ophthalmoplegia* peripheral neuritis ataxia and clouding of consciousness is another syndrome which is thought to represent deficiency of thiamine and other B vitamins

Administration of thiamine in conjunction with other vitamins of the B complex, is of value in the treatment of delirium tremens and of other acute alcoholic psychoses

*Laboratory tests** are of great assistance in the diagnosis of thiamine deficiency The concentration of pyruvic acid in the blood may be increased above 1 3 mg per 100 cc which is the upper limit of normal in the basal state A better test is measurement of pyruvic acid lactic acid and glucose in the blood after mild exercise and the ingestion of glucose (Horwitt) The glucose tolerance test may show a diabetic type of curve The excretion of thiamine in the urine after giving a test dose either orally or parenterally is reduced in thiamine deficiency

Treatment The diet should be high in thiamine and other factors of the B complex since multiple deficiency is the rule There are only a few foods which are rich sources of thiamine namely peas beans lean pork peanuts oatmeal whole wheat and enriched flour and bread Other foods however, may contribute significantly to the thiamine intake, such as milk, vegetables and fruits Significant amounts of thiamine may be lost in the preparation of food due to its solubility in water and ready destruction by moist heat Boiling of vegetables may lead to losses of 20–50 per cent depending on whether or not the water is discarded Roasting may destroy as much as 40 per cent of thiamine broiling 30 per cent, frying 15 per cent.

In mild thiamine deficiency 5 mg of the vitamin should be administered orally three times daily In beriberi heart disease 20–50 mg should be given parenterally two to three times daily either by the intravenous or intramuscular route After the first few days, oral administration may be substituted, 10 mg three times daily being sufficient In peripheral neuritis a similar oral dose is usually effective When amounts larger than 10 mg are given by mouth in a single dose most of the additional quantity is unabsorbed Treatment should be continued until maximum restoration of function has been attained After the first few weeks 5 mg three times daily should be adequate therapy

In beriberi heart disease, diuresis often will be noted within twenty four to forty eight hours after beginning therapy and the patient will appear markedly improved Within a few weeks the heart will return to normal size and electrocardiographic abnormalities will disappear in most patients At times treatment must be continued for several months Digitalis is of little benefit in heart disease due to thiamine deficiency

In polyneuritis pain usually subsides within the first few days although burning paresthesias may persist for weeks If the neuritis has not been too extensive or lasted too long complete restoration of function can be expected but it may be necessary to continue treatment for three to six months Physiotherapy is of considerable assistance in restoration of function*

In treating patients who have diseases in

* See also Chapter 48

* See also Chapter 45

diabetes mellitus and in cirrhosis of the liver Defective utilization may be the explanation in both of these conditions

The administration of sulfonamide drugs and of antibiotics may decrease synthesis of vitamins by bacteria in the intestinal tract and perhaps have an effect on utilization or destruction in the tissues

Thiamine

Thiamine or vitamin B_1 functions in intermediate carbohydrate metabolism as the coenzyme cocarboxylase In thiamine deficiency pyruvic acid accumulates in the blood and the tissues This finding may be used in the evaluation of thiamine nutrition

The recommended daily allowance of thiamine is 1 2–1 8 mg for an average adult man 1 0–1 5 mg for an adult woman Requirement is increased during growth and in pregnancy and lactation It is also greater during fever hyperthyroidism and other conditions associated with increased metabolism

Thiamine Deficiency Thiamine deficiency is commonly seen in the United States in patients with chronic alcoholism and cirrhosis of the liver and less often in diarrheal diseases in hypermetabolic states and postoperatively when glucose has been administered parenterally as the sole source of nutriment It is also not rare in advanced neoplasia and in other conditions associated with marked anorexia The peripheral neuritis of pernicious vomiting of pregnancy of chronic alcoholism and of pellagra are due to thiamine deficiency Diabetic neuritis is only occasionally related to lack of thiamine

Early signs of thiamine deficiency consist of anorexia fatigability and certain mental and personality disturbances Irritability vague fears moodiness depression quarrelsomeness lassitude and lack of ambition are among the more common findings In more advanced deficiency polyneuritis cardiovascular disturbances edema occur

Early evidence of *polyneuritis* consists of numbness tingling and burning of toes or soles of the feet shooting pains in the feet and legs pretibial anesthesia, and calf muscle tenderness Somewhat later weakness of the muscles anesthesia of the feet and legs reduction of the Achilles and patellar reflexes and atrophy of the leg muscles are noted Edema is frequently associated with the neuritis The upper extremity is rarely involved until late in the course of the disease

The cardiovascular disturbances of thiamine deficiency, or *beri beri heart disease,* are much less definitive Signs of left or right sided heart failure or both, may be noted although a predominance of signs of right sided failure has been reported Death may occur suddenly from acute peripheral circulatory collapse Cyanosis a wide pulse pressure and a relatively normal circulation time in the presence of congestive heart failure are important findings The heart is enlarged usually both to the right and left Systolic or occasionally diastolic murmurs may be present and either a tic tac or gallop rhythm is often noted Edema may be massive and transudation into serous cavities may occur

Electrocardiographic abnormalities are found early but are nonspecific—consisting of T wave changes prolonged Q T interval lowering of the QRS complexes, and at times shifts in the S–T segment and abnormalities of the P waves

Diagnosis is dependent on a dietary history indicative of low thiamine intake absence of the common etiologic factors in the production of heart disease, and a combination of some of the findings noted above Mild polyneuritis may be an associated sign of great diagnostic assistance A therapeutic test may corroborate the diagnosis since beriberi heart disease improves

Estimation of the concentration of riboflavin in the blood or determination of the excretion in the urine may be of some assistance in diagnosis Lesions which are due to riboflavin deficiency should respond fairly rapidly to treatment and this finding is of corroborative diagnostic value

Treatment In the treatment of riboflavin deficiency, a diet rich in riboflavin containing foods together with supplements of the vitamin are prescribed In most instances, 5 mg of riboflavin given orally three times a day will be sufficient to promote resolution of the lesions Subjective complaints disappear within a few days The angular stomatitis and cheilosis heal within a week or two and red cells disappear from the corneal vessels The glossitis improves more slowly and the skin gradually returns to normal In occasional patients as much as 30 mg of riboflavin daily may be needed for adequate therapy In the presence of gastrointestinal abnormalities or when oral feeding is undesirable 5–10 mg of riboflavin may be given intramuscularly or intravenously once or twice daily

The most important dietary sources of riboflavin are milk cheese liver eggs and green vegetables One serving of liver will fulfill the recommended daily allowance and one quart of milk will meet the minimal daily requirement Little riboflavin is destroyed in the pasteurization or bottling of milk but much may be lost on exposure to light Riboflavin is fairly stable in ordinary cooking procedures such as roasting or broiling although some is lost in the water in which vegetables are cooked

In cases of riboflavin deficiency the diet should be high in protein and in all of the vitamins of the B complex as well as in riboflavin because of the metabolic interrelationships of the B vitamins and of riboflavin and protein In addition most of the deficiency states are multiple in nature

Niacin

Niacin (nicotinic acid), the pellagra preventive factor, functions in the body as a component of two important coenzymes coenzyme I or cozymase and coenzyme II, both of which are concerned in glycolysis and tissue respiration

A relationship between the metabolism of niacin and the amino acid tryptophan has recently been discovered When tryptophan is administered a portion of it is converted to niacin and there is an increase in the urinary excretion of niacin derivatives Large doses of tryptophan have been shown to be effective in the treatment of pellagra These findings explain at least in part the occurrence of pellagra in association with diets high in corn Not only is corn low in niacin but the main protein of corn zein, is low in tryptophan Although milk and eggs contain little niacin
they are effective pellagra preventive food
due to good tryptophan content

The daily requirement of niacin has no
been determined due to the complexit
of metabolism just noted and to other dif
culties in conducting balance experimen
The Food and Nutrition Board tentativ
recommends an allowance of 10–18
daily for adults

Diagnosis Classical *pellagra* is a
disease in the United States but mild n
deficiency is not uncommon The
manifestations include anorexia lassi
glossitis diarrhea and various nonsp
psychic changes Cheilosis and an
stomatitis may also occur The tong
comes sore red often swollen with
trophy or atrophy of the papillae
psychic changes include anxiety irrit
forgetfulness and depression whil
sions hallucinations disorientatio
fusion and stupor occur later in the
Diarrhea is watery in type and
associated with proctitis

The characteristic dermatitis o
involves exposed surfaces of the

which thiamine requirement is increased such as long continued febrile illnesses (e g tuberculosis typhoid fever rheumatic fever subacute bacterial endocarditis) or hyper thyroidism the administration of thiamine in amounts of 5–10 mg daily may prevent deficiency from occurring In the presence of suggestive evidence of deficiency the dosage may be increased to 5 10 mg three times daily In diseases involving disturbances of digestion or absorption of food thiamine should be given parenterally

Riboflavin

Riboflavin functions in the body as a constituent of several important enzymes in tissue respiration The requirement of riboflavin appears to be related to body size rather than to caloric intake and the recommended daily allowance is 1 5 mg for adult women 1 8 mg for adult men Somewhat larger quantities are suggested during periods of rapid growth and throughout pregnancy and lactation

Abnormalities of riboflavin metabolism may exist in association with severe injuries burns hemorrhages and infection Whether utilization is interfered with or requirement is increased is not known A relationship has been demonstrated between the retention of riboflavin and the retention of protein

Riboflavin Deficiency Riboflavin deficiency often occurs in association with niacin deficiency and until recently the characteristic manifestations have been considered part of the clinical picture of *pellagra* Signs of riboflavin deficiency are frequently encountered in the course of prolonged febrile illnesses such as rheumatic fever subacute bacterial endocarditis typhoid fever and tuberculosis Even in acute febrile diseases characteristic lesions may be observed In malignancy hyperthyroidism long standing heart disease with failure cirrhosis of the liver diabetes mellitus and gastrointestinal diseases associated with vomiting and diarrhea riboflavin deficiency is a frequent finding

Deficiency is much more common in older age groups even in the absence of any of the above conditions Anorexia food idiosyncrasies and environmental factors may limit the intake of riboflavin in this group

Diagnosis Riboflavin deficiency should be suspected in persons who complain of soreness of the lips and tongue photophobia burning of the eyes and lacrimation and who show several of the characteristic physical findings such as cheilosis angular stomatitis glossitis a seborrheic type of dermatitis or superficial vascularization of the cornea None of these lesions is pathognomonic of riboflavin deficiency but the occurrence of several of them in association with a disease which may affect riboflavin metabolism or a history of a low riboflavin intake makes the diagnosis more likely

The lesions of the lips (swelling redness and denudation at the line of closure) often resemble ordinary chapping from weather Redness maceration crusting and fissures at the angles of the mouth occur in association with malocclusion poorly fitting dentures and in deficiency of vitamins other than riboflavin The seborrheic dermatitis of riboflavin deficiency is found particularly in the nasomalar and nasolabial folds at the outer canthi of the eyes behind the ears and on the scrotum

Vascularization of the cornea occurs following trauma infection and probably in association with deficiency of several of the essential nutrients The glossitis of ariboflavinosis is difficult to distinguish from that of deficiency of niacin folic acid iron or vitamin B_1 Changes in the papillae of the tongue occur in each of these deficiency states A purple or magenta color is more common in riboflavin deficiency but this is of minor assistance

eral, three to five times the quantity suggested as a maintenance allowance of a vitamin should be sufficient for adjuvant therapy The anemia of pellagra may respond to iron if it is hypochromic in type, to folic acid if it is macrocytic

Acute pellagra responds rapidly to therapy The mental symptoms clear up in one or two days, the tongue becomes less sore and swollen, diarrhea ceases, and skin lesions look improved It may require several weeks for restoration of the skin to normal or for regeneration of lingual papillae In long standing, chronic niacin deficiency, the dermatitis and glossitis undergo resolution more slowly and several months may be required for a return to normal

Lesions of the tongue which cannot be definitely attributed to niacin deficiency may at times be favorably influenced by giving 200–600 mg of niacin daily for many months Glossitis may be the result of deficiency of any one of several nutrients at times riboflavin, folic acid vitamin B_{12}, or iron promotes healing In other instances, the whole vitamin B complex must be given before restoration is achieved There are some types of glossitis which are unrelated to nutritional deficiency

Niacin seems to be of some benefit, in conjunction with thiamine in the treatment of delirium tremens It has not proved of value in the treatment of a number of diseases which have no demonstrable relationship to nutritional deficiency, such as eighth nerve deafness, multiple sclerosis irradiation sickness, and acne vulgaris

The use of niacin (nicotinic acid) as a vasodilating agent in the treatment of Ménière s syndrome* and of angina pectoris† is pharmacologic rather than nutritional therapy and will not be discussed here

* See Chapter 20
† See Chapter 10

Pyridoxine or Vitamin B_6

Pyridoxine has been shown to function as part of several enzyme systems in the metabolism of amino acids The human requirement is unknown Deficiency has been produced experimentally by the administration of an antagonist, desoxypyridoxine Findings included seborrhea like skin lesions, fissures at the angles of the mouth and lateral canthi of the eyes, and sore, swollen, red tongues and buccal mucous membranes Pyridoxine deficiency due to dietary inadequacy is unlikely because of the wide distribution of this vitamin in foods

Therapy with pyridoxine has been reported to bring about healing of cheilosis in certain instances Pyridoxine has been administered in large doses, as much as several hundred milligrams daily, in the treatment of radiation sickness and of nausea and vomiting of pregnancy The beneficial results reported by some workers have not been substantiated by others Pyridoxine has been thought to be of value in severe granulocytopenia

Pantothenic Acid

Pantothenic acid has been shown to function in the process of acetylation, as a coenzyme, but little is known about its importance in human nutrition No symptoms of deficiency have been recorded and the requirement has not been determined Although graying of the hair occurs in pantothenic acid deficiency in certain animals pantothenic acid is of no value in the prevention or treatment of gray hair in man

Choline

Choline is an important member of the vitamin B complex which may function in the body in at least three ways in the formation of phospholipids, as acetyl choline, and in supplying labile methyl groups in association with methionine and

genitalia, bony prominences, areas subjected to trauma or irritation, and skin folds It is bilateral, symmetrical, clearly demarcated from normal skin and resembles sunburn in the early stages Bleb formation secondary infection and brownish pigmentation occur later In chronic pellagra, only pigmentation and thickening of the skin may be evident

Severe inflammation of the entire gastrointestinal tract is characteristic of acute episodes and vaginitis is an accompanying finding Deficiency of riboflavin may complicate the clinical picture and thiamine deficiency is common Anemia, either macrocytic or hypochromic, and achlorhydria are frequently associated findings

A neurologic syndrome, which may represent acute severe niacin deficiency, has been described consisting of progressive stupor grasping and sucking reflexes and cogwheel rigidity of the extremities These findings may occur alone or in association with glossitis and other evidence of an inadequate supply of niacin

The diagnosis of niacin deficiency in the absence of characteristic skin lesions depends on the presence of glossitis, diarrhea and/or mental changes in a person whose diet has been low in niacin and in good protein A low level of N′ methyl nicotinamide in the urine may be of assistance in diagnosis

Niacin deficiency occurs secondary to a number of diseases which interfere with the intake, absorption or proper utilization of food, or which increase the requirement of niacin Among the important contributory causes are chronic alcoholism carcinoma, diarrheal states cirrhosis of the liver, and prolonged febrile illnesses

Treatment It is obvious that therapy should consist of the administration of a diet rich in good protein as well as in niacin In acute pellagra it may be necessary to administer a liquid or very soft diet at first because of the stomatitis and digestive disturbances Milk, eggs, and vegetable purees may be given initially lean meat, glandular organs, green vegetables, and fruit should be added as symptoms improve The caloric intake should be high, as much as 3500–4500 calories after the first few days, since weight loss has often been severe The best sources of niacin are liver, yeast, lean meats, and whole wheat while peanuts, legumes and potatoes are fair sources Milk and eggs should be used in generous amounts due to their high tryptophan content

In addition to dietotherapy, the patient with acute pellagra should receive niacinamide in amounts of 0 3–0 5 Gm daily given in divided doses of 50–100 mg each If oral administration is impossible niacinamide may be given either intravenously or intramuscularly, in divided doses of 0 1 Gm two or more times daily In mild niacin deficiency, the administration of 50 mg of niacinamide three times a day will be adequate

Niacinamide is the preparation of choice, rather than nicotinic acid since the latter may produce vasodilating reactions which, although not harmful are unpleasant and may alarm the patient Nicotinamide should always be used for parenteral therapy The use of nicotinic acid intravenously in other than dilute solution and in amounts exceeding 25 mg is dangerous

In addition to niacinamide and a diet high in calories and protein patients with pellagra should receive some source of the entire vitamin B complex such as yeast liver extract or vitamin B complex tablets Powdered brewers yeast may be given twice daily in 15–30 Gm doses It may be taken in tomato juice or in milk flavored with chocolate or vanilla Liver extract may be given parenterally, 2 cc daily If vitamin B complex tablets or fortified yeast tablets are used the dose is dependent on the quantity of vitamins in the tablet and the severity of the patient s need In gen

Vitamin B_{12} Cyanocobalamin*

Vitamin B_{12} is a cobalt complex whose structure is still incompletely known This vitamin appears to be the antipernicious anemia factor of liver and is identical or very similar to the extrinsic factor of Castle The intrinsic factor of Castle which is present in normal gastric juice and absent from the gastric juice in pernicious anemia, seems to facilitate, in some way the ab sorption or utilization of vitamin B_{12}

Vitamin B_{12} is an extremely potent substance One microgram given daily parenterally will effect a reticulocyte response, blood regeneration, and the return of megaloblastic bone marrow to normal in pernicious anemia It is also effective in the treatment of the neurologic lesions of pernicious anemia The optimal dosage has not been established, but the administration of 30 μg parenterally once a week appears to be satisfactory for initial therapy Larger amounts and more frequent injections may be desirable in the presence of neurologic lesions The maintenance dose is probably 1–2 μg (micrograms) per day in most patients

Vitamin B_{12} has also been shown to be effective in the treatment of the macrocytic anemia of sprue in nutritional macrocytic anemia, and, in some instances in macrocytic anemia of pregnancy

Ascorbic Acid

Ascorbic acid is important in the formation of intercellular substance in tissues of mesenchymal origin and appears to have a role in the metabolism of the amino acids tyrosine and phenylalanine It may also be related to the activity of the adrenal cortex Recently a metabolic relationship between ascorbic acid and folic acid has been demonstrated Whether ascorbic acid functions in a specific enzyme system in the body has not been established

The amount of ascorbic acid which will prevent scurvy in an adult is est[imated to] be 15–30 mg per day The allowan[ce recom]mended by the Food and Nutritio[n Board] is considerably higher, 70–75 mg It seems advisable to recommend a g[enerous] allowance of ascorbic acid for a num[ber of] reasons Experiments in guinea pig[s have] shown that more ascorbic acid is n[eeded] for normal healing of wounds, n[ormal] tooth development, and maximal resis[tance] to injury by bacterial toxins than i[s re]quired for the prevention of scurvy Nu[mer]ous conditions are associated with an [in]creased requirement of ascorbic a[cid], including pregnancy and lactation, hype[r]metabolic states (such as hyperthyroidis[m] and prolonged febrile illnesses), and prob[ably] certain allergic states, severe burns and other types of serious injury A decrease in the concentration of ascorbic acid in the plasma has been noted in infectious diseases such as tuberculosis, pneumonia, osteomyelitis, whooping cough, diphtheria, rheumatic fever, bronchiectasis, and rheumatoid arthritis There is some evidence that ascorbic acid may be related to immunologic mechanisms, and it has been reported to be of value in the prevention of allergic reactions following the intravenous administration of arsenical preparations

Ascorbic acid is important in the healing of wounds as has been clearly demonstrated in experimentally induced human scurvy Abnormalities of ascorbic acid metabolism which have been noted in severe burns may be dependent on an increased demand for repair of tissue

Poor absorption of ascorbic acid occurs in diarrheal diseases while in achlorhydria or following the administration of alkali ingested ascorbic acid may be destroyed in the intestinal tract The administration of certain drugs increases the urinary excretion of ascorbic acid

Certain therapeutic diets are low in ascorbic acid In the Sippy regime, which has been widely used in the treatment of

* See also Chapter 14

betaine In animals, choline deficiency causes fatty livers and hemorrhagic lesions in the kidney and, if deficiency persists cirrhosis of the liver develops

The choline requirement is difficult to ascertain since it is partially dependent on the methionine and betaine content of the diet Elvehjem suggests that it is probably less than 0 5 Gm daily, which may be furnished by the average diet The best sources are egg yolk, soy bean meal, liver, dried yeast, pancreas, brain, and kidney

Choline has been used in the treatment of liver disease in conjunction with other vitamins and a diet high in protein and carbohydrate Favorable results have been reported in cirrhosis of the liver and in toxic hepatitis The usual dose is 3–6 Gm daily Methionine has also been used in the therapy of cirrhosis as have other so called lipotropic agents

Inositol

Little is known of the specific function of inositol or its role in human nutrition It appears to prevent the development of certain types of fatty liver in animals and has been suggested as an adjuvant in the prevention and treatment of fatty livers and cirrhosis in man Inositol may be effective in lowering serum cholesterol in hypercholesteremic states The tentative dosage is 10 Gm three times daily

Folic Acid*

Folic acid or pteroylglutamic acid is a factor required for growth and for the formation of blood by several species of animals In addition to its presence in food in free and combined form it is synthesized by bacteria in the intestinal tract Folic acid has been shown to be a potent hematopoietic agent in various types of human macrocytic anemia The human requirement of folic acid is unknown but on the basis of animal studies may be in the neighborhood of 0 1–0 2 mg per day Good sources of folic acid are liver, deep green leafy and other vegetables cauliflower, kidney, muscle meat, and wheat cereals Recently a metabolite of folic acid has been isolated, citrovorum factor or folinic acid, which may be an active form of this vitamin

* See also Chapter 14

Folic Acid Therapy Folic acid has many of the effects of the erythrocyte maturation factor of liver, which recent investigation has shown to be vitamin B_{12} Administration of folic acid is followed by regeneration of blood and return of the bone marrow to normal in patients with pernicious anemia, macrocytic anemia of pregnancy, nutritional macrocytic anemia, sprue, megaloblastic anemia of infancy, and the macrocytic anemia which follows gastrectomy Folic acid will not prevent or relieve the neurologic lesions which occur in pernicious anemia In sprue, the administration of folic acid leads to improvement in absorption of glucose, fat, and fat soluble vitamins from the intestinal tract Steatorrhea is diminished but an excess of fatty acids in the stool may persist

Indications for the therapeutic use of folic acid in the *macrocytic anemias* gradually are being clarified Folic acid appears to be the therapy of choice in macrocytic anemia of pregnancy and megaloblastic anemia of infancy, which anemias are often refractory to vitamin B_{12} Some patients with nutritional macrocytic anemia and sprue respond more satisfactorily to therapy with folic acid than with vitamin B_{12} In treating pernicious anemia, vitamin B_{12} is obviously the preferable vitamin since folic acid will not prevent the development of lesions of the spinal cord

When folic acid is used in the treatment of macrocytic anemia it should be given orally in amounts of 5–10 mg three times a day until blood regeneration is complete A daily dose of 5 mg is usually satisfactory for maintenance therapy

administered in high dilution by intravenous drip

It has been suggested that 1–2 Gm of ascorbic acid be prescribed daily in severe burns or other serious tissue injury Similar quantities are advisable in the preoperative preparation, or postoperative treatment, of patients whose tissues have been seriously depleted of ascorbic acid

Ascorbic acid may be of value in the therapy of gingivitis in conjunction with local measures if the patient is shown to have deficient tissue stores of this vitamin

In planning therapeutic diets, if sufficient ascorbic acid–containing foods cannot be included the difference in recommended daily allowances should be met by administering pure ascorbic acid

Treatment with ascorbic acid should be continued until all signs of deficiency have disappeared and/or until the condition causing an increase in requirement or metabolic abnormalities has been relieved

VITAMIN D

Vitamin D consists of a group of substances the two most important members of which are vitamin D_2 (activated ergosterol, calciferol or viosterol) and vitamin D_3 (activated 7 dehydrocholesterol) The latter occurs in fish liver oils and is the compound presumably formed in human skin

Vitamin D promotes the mineralization of bone by increasing the permeability of the intestinal mucosa to calcium salts which leads to an increase in serum calcium, this in turn results in diminished activity of the parathyroid gland and consequently a decrease in the rate of phosphate excretion by the kidney Vitamin D also seems to have a direct effect on the calcification of growing bone

Normal bone formation requires an adequate supply of calcium and phosphorous as well as vitamin D If the diet is severely restricted in calcium and phosphorous bones will be deformed and with an abundant supply of vi

It is customary to express the content of preparations in term national Units one unit being e to the activity of 0 025 µg of calcif daily requirement of vitamin D tain, since the amount which synthesized in the skin as a resul posure to daylight is unknown alth appears to be small It is recommend 400 International Units be supplied during infancy, throughout the peri growth, and during pregnancy and tion The average adult probably r little, if any, supplemental vitamin D persons working at night for those wh habits preclude exposure to sunlight for elderly persons, small suppleme would appear to be desirable

Diagnosis of Vitamin D Deficiency

A deficiency of vitamin D leads to the development of rickets in infancy or childhood and to osteomalacia in adult life While severe rickets and osteomalacia are rare in the United States rickets of mild or moderate severity is not uncommon and minimal abnormality of bone, demonstrable only by histologic examination is probably frequent

Manifestations of rickets in infancy include restlessness irritability, excessive sweating about the head and neck, muscle weakness, digestive disturbances due to impaired intestinal motility and often delayed dentition Physical findings include open fontanels, square head chest deformities rachitic rosary and protuberant abdomen Changes in certain of the long bones occur as a result of the action of muscle pull on imperfectly calcified bone The deformity is increased by the weight of the body when the child is walking

Tetany due to low serum calcium concentration often complicates the clinical picture of rickets and the characteristic

peptic ulcer, the diet recommended for the first week of therapy contains about 5 mg of the vitamin per day, and for the fourth week about 15 mg Diets prescribed for persons suffering from gallbladder disease other gastrointestinal disturbances or allergy, are likewise often deficient in ascorbic acid

Evidence of ascorbic acid deficiency should be sought in the above conditions and the *administration of ascorbic acid* in amounts greater than the allowance recommended for health appears to be indicated

Diagnosis of Ascorbic Acid Deficiency

Manifestations of ascorbic acid deficiency in the adult include easy fatigability pains in the muscles and joints hyperkeratosis of hair follicles with perifollicular hemorrhages, redness and swelling of the gums with bleeding on slight pressure poor healing of wounds and at times anemia and edema Hemorrhages in the skin subcutaneous tissues and muscles are common in advanced scurvy and may occur in serous cavities from any of the mucous membranes or in any organ of the body In infantile scurvy subperiosteal hemorrhages are characteristic and pathologic changes in the bones are noted

The diagnosis of ascorbic acid deficiency in its incipiency is dependent on *laboratory tests* The concentration of ascorbic acid in the plasma reflects dietary intake a level of greater than 0.7 mg per 100 cc indicates normal nutrition A concentration of less than 0.3 mg per 100 cc suggests a dietary intake of less than 25 mg daily but does not indicate the degree of depletion of bodily stores of ascorbic acid In order to determine this some type of load or saturation test must be given or the ascorbic acid content of the white cell platelet layer of the blood may be measured

Ascorbic acid cannot be found in the plasma in the presence of scurvy nor in some persons who do not show clinical signs of ascorbic acid deficiency The concentration in the white cell platelet layer reaches zero just before definite clinical evidence of scurvy appears

Load tests for evaluating ascorbic acid nutrition consist of administration of a test dose of this vitamin either orally or intravenously, and measurement of the urinary excretion or concentration in the blood for several hours thereafter

If laboratory procedures are not available for assistance in the diagnosis of ascorbic acid deficiency the history of a poor diet and the presence of suggestive physical signs and of conditions known to predispose to such deficiency must suffice The capillary fragility test is not of any value in the diagnosis of ascorbic acid deficiency

Treatment The diet, whenever possible should include foods high in ascorbic acid such as citrus fruits (oranges grapefruit lemons), tomatoes green leafy vegetables cabbage, green pepper, collards brussels sprouts, strawberries and other green and yellow vegetables and fruits Ascorbic acid is readily soluble in water and rapidly destroyed by heat and oxidation Accordingly much of the vitamin is lost in the process of cooking or is discarded in the water Little ascorbic acid is destroyed in the canning process or during cold storage of citrus fruits

For mild uncomplicated ascorbic acid deficiency in adults 50–100 mg of the vitamin should be administered three times daily by mouth in addition to the diet described above Similar amounts are useful *in febrile diseases and in hypermetabolic states* For severe deficiency 0.5–1.0 Gm should be given daily in divided doses of 0.1–0.2 Gm The oral route is satisfactory if there is not any gastrointestinal disturbance If necessary vitamin C may be given either intravenously or intramuscularly For parenteral use, a sodium salt is preferable to the free acid which if used, should be

which has been fortified with vitamin D can be used in the prevention and treatment of rickets, but should not be relied upon as the sole antirachitic measure because of its low potency

Rickets which is refractory to treatment has been reported especially in children over 3 years of age Usually there is an associated abnormality of mineral metabolism Massive doses of vitamin D may be of assistance in these instances

Severe toxic reactions can occur from the use of large doses of vitamin D over long periods of time Manifestations include an elevation of serum calcium, metastatic calcification, renal failure, and death Associated findings are loss of weight, vomiting and diarrhea Intoxication can be detected at an early stage if serum calcium is determined frequently whenever patients receive large amounts of vitamin D If the level increases above 11 mg per 100 cc medication should be discontinued

Vitamin D has been used in the treatment of a number of conditions other than rickets, among them *arthritis, psoriasis* and *pemphigus* The therapeutic value in these diseases is doubtful In arthritis massive doses of 200 000 to 300 000 International Units daily have been prescribed While benefit has been reported in some patients so treated the danger of toxic reactions is great

There is considerable evidence that large doses of vitamin D are of value in the treatment of cutaneous *tuberculosis* Doses of 100 000 or more units daily are prescribed for many months Patients should be frequently checked for evidence of toxicity

Vitamin D has been given, in prophylactic or small therapeutic doses to persons suffering from *fractures* and to those who have had operations on bone Such administration seems logical to ensure an adequate supply of this vitamin for the healing process and for the deposition of normal bone

VITAMIN E

Vitamin E has not, as yet, b strated to be essential in human In animal experiments, vitamin E has resulted in sterility, changes muscles, and paralysis In humans E has been used in the preve spontaneous abortion with equiv sults It has not proved effective treatment of muscular dystrophies sitis, or sclerosing diseases of the cord Vitamin E has been given to p with angina pectoris, congestive failure, and hypertension but in a nu of carefully controlled studies no nificant improvement has been der strated

VITAMIN K

Numerous compounds with vitamin activity have been discovered Naturall occurring vitamin K is fat soluble It essential for the formation of prothrombin which is a necessary factor in the coagulation of blood The formation of prothrombin takes place in the liver but the exact role of vitamin K in this process is unknown In severe liver disease there is a decrease in prothrombin in the blood which is not affected by the administration of vitamin K This finding has been used as the basis of a test of liver function The daily requirement of vitamin K is unknown, but is usually satisfied by any good diet in addition to the amount synthesized by bacteria in the intestinal tract It has been suggested that the requirement of the infant is about one microgram daily Foods which contain considerable amounts of vitamin K include spinach, kale, cabbage, cauliflower, tomatoes egg yolk and some of the vegetable oils

One critical period in life when an extra supply of vitamin K is needed is when the infant is in utero and for the first few days after birth The pregnant woman rarely receives sufficient vitamin K to prevent a

carpopedal spasms or convulsive seizures, make their appearance

In the early diagnosis of rickets, determination of alkaline serum phosphatase is of great value* In infants and young children, elevation of serum phosphatase above the normal of 5–15 Bodansky units is highly suggestive evidence of rickets, since few other conditions influencing phosphatase activity occur in this age group

Osteomalacia is particularly apt to occur during pregnancy and lactation and is characterized by tetany, osteoporosis, and bending and fracture of bones Osteoporosis and tetany also occur in association with steatorrheas such as sprue and the celiac syndrome Vitamin D, as well as calcium is poorly absorbed in these conditions In osteomalacia the concentration of blood calcium will be low, less than 9 mg per 100 cc, and alkaline phosphatase will be above the normal adult level of 3–5 Bodansky units Since there are a number of diseases in adults which affect phosphatase in the blood a high level must not be interpreted as evidence of osteomalacia without evaluation of associated findings

Prevention and Treatment

The prevention of rickets can be attained by the administration of 400 International Units of vitamin D daily except in the rare instances of abnormal mineral metabolism It is customary to prescribe somewhat larger doses such as 800–1200 units and it may be advisable to provide these amounts, at least for premature infants *Cod liver oil USP contains about 400* IU of vitamin D per teaspoonful, halibut liver oil and percomorph oil somewhat larger quantities Fish liver oils are preferable to other vitamin D preparations in infancy since they furnish vitamin A as well as vitamin D Preparations containing only vitamin D are available viosterol in oil and calciferol (drisdol in propylene glycol) Both contain 10 000 International Units of vitamin D per Gm or approximately 222 IU per drop Calciferol is readily miscible in water These preparations may be used where the question of allergy to fish liver oils is a problem or in older age groups when palatability becomes important Some pediatricians prefer to use massive doses of vitamin D such as 250 000 IU twice yearly for the protection of infants against rickets For this purpose purified preparations of vitamin D_2 or D_3 which contain 40,000 International Units per Gm are available

It is probably advisable to give 400 IU of vitamin D to all children until growth has been completed and similar quantities should be administered to all women throughout pregnancy and the period of lactation In adults concentrates of vitamin D may be given in capsule or liquid form Many of these preparations contain vitamin A as well as vitamin D The physician should inspect the preparation chosen for both standardization and unitage and judge his dosage accordingly

For the cure of rickets the amount of vitamin D prescribed is dependent on the age of the child and severity of the disease The dose in infancy is usually 1200 IU daily but as much as 20 000 IU may be given in refractory rickets Reports of the cure of rickets by a single large oral dose of 600 000 IU of vitamin D have appeared and toxicity has not been noted with this therapy

Treatment often must be prolonged, five *or six months being required for complete* healing which is determined by serial roentgenograms of the bones and by return of alkaline serum phosphatase to normal The improvement which may occur in bony deformities is often remarkable

There are few foods which supply vitamin D in the ordinary diet Small amounts are present in butter, eggs, mammalian liver, milk and milk products Milk

* See Chapter 48

TABLE 48 SUGGESTIONS FOR NUTRITIONAL THERAPY IN VARIOUS DISEASE STATES*

Disease	*Therapeutic diet*	*Rationale*
Addison's	High carbohydrate, salt	NaCl excretion high. Hypoglycemia
Alcoholism		
Acute	Soft, high calories, vitamins, esp thiamine niacin	Poor food intake
Chronic	High protein, B vitamins	Poor food intake
Allergy	Provide all essential nutrients	Nutrient deficiency common on restricted diets
Anemias		
Blood loss	Transfusion, iron	Replacement
Erythroblastic	High protein, vitamin, low carbohydrate, *fermentable nutrients*	Protein and B_{12} needed for blood *formation*
Nutritional	High protein, B complex, folic acid, B_{12}	Deficiency folic acid or B_{12}
Sickle cell	6-meal diet, low fat, no overeating	
Constipation	Equal amounts of food in each meal Fruit, roughage, bulk as tolerated	Stimulate peristalsis
Diarrheal states		
Acute	Low residue, clear fluids, 200 cc /hour	Replace fluid loss, avoid irritants
Chronic	*Bland*, low residue, *B* vitamins	Avoid irritants, *B* vitamin deficiency common, often absorption defect
Colitis	Bland, high protein, low residue and fat No raw fruits or vegetables Vitamins esp B complex, occasionally fat soluble	Avoid irritants, excessive loss of nutrients
Ileitis	Similar to colitis Oral protein hydrolysates	Absorption defect, excessive loss of nutrients
Gallbladder disease		
Chronic cholecystitis	Low fat, cholesterol Calories to optimum weight, no overeating Olive oil, *cream, butter allowed*	Indigestion with fat Cholesterol a constituent of gallstones
Chronic noncalculous	High fat (to tolerance)	Stimulate emptying gallbladder
Heart failure (congestive)	Adequate calories, protein, and vitamins, low salt	Anorexia, poor absorption and utilization, edema
Heat cramps	Salt	Salt lost in sweat
Hemophilia	High protein, ascorbic acid	
Hepatic disease	*High protein, carbohydrate, moderate* fat B vitamins, esp choline, inositol, vitamin B_{12}, folic acid, methionine	*Protect liver, prevent* fatty infiltration, promote fat transport
Cirrhosis, portal	As above plus low salt	
Primary biliary	Vitamin K	*Poor absorption*, vitamin K
Hypertension	No overeating, low salt	Avoid obesity
Hypermetabolic	High calories, protein, B vitamins, ascorbic acid	Nutrient requirements increased
Febrile illness, chronic	Attractive supportive diet with supplements B vitamins, ascorbic acid	Same as above
Hyperthyroidism	Supplements thiamine, riboflavin, niacin, ascorbic acid	Same as above
Tuberculosis	High calcium and vitamin D in addition to above	Same as above

* These suggestions should be supplemented by the diets provided in other chapters for specific diseases *More detailed rationale* will be found in the discussion of the individual diseases.

fall in the prothrombin concentration in the infant's blood during the first week of life Recent evidence suggests that vitamin K may function in other ways than in the formation of prothrombin Lesions have been found in the blood vessels and brain substance of infants deficient in prothrombin prior to the appearance of hemorrhage

Vitamin K Deficiency

A dietary deficiency of vitamin K is rare since this factor is present in a large variety of foods and is synthesized in the intestinal tract Since naturally occuring forms of vitamin K are fat soluble deficiency is usually found in association with diseases in which fat absorption is impaired Such diseases include obstructive jaundice biliary fistula and the steatorrheas such as sprue the celiac syndrome and pancreatic fibrosis Poor absorption of vitamin K may also occur in ulcerative colitis regional ileitis and other severe diarrheal states and following operations on the intestinal tract in which large areas of absorptive surface have been removed or short circuited It seems likely that vitamin K deficiency may occur following the administration of certain antibiotics due to a depression of intestinal synthesis

Clinical signs of vitamin K deficiency are easy bruising and hemorrhage Diagnosis is dependent on estimating the prothrombin activity of the blood A number of tests are available for this purpose all of them dependent on indirect estimation of prothrombin concentration

Prothrombin time is prolonged by dicumarol which is widely used in the control of diseases causing thrombosis * Decreased prothrombin activity has been reported following large doses of salicylates

Prevention and Treatment Vitamin K deficiency in the newborn will be prevented if the mother receives a daily supplement of 1 mg in the last month of pregnancy If this has been done it is unnecessary to administer vitamin K to the infant after birth If a supplement is not prescribed during pregnancy 1–5 mg of vitamin K should be given to the mother prior to delivery In lieu of this the infant should receive 1 mg of vitamin K after birth which amount will be sufficient until food is taken

The treatment of vitamin K deficiency in conditions other than the newborn consists of the daily administration of 5–10 mg of menadione or of one of the water soluble preparations of vitamin K such as 4 amino 2 methyl 1 naphtholhydrochloride If menadione or some other fat-soluble compound is used bile salts in 1 Gm amounts should be given with the vitamin to ensure absorption If the disease responsible for hypoprothrombinemia is one involving the absorptive surface of the small intestine or if there is contraindication to oral therapy vitamin K may be given intravenously or intramuscularly Water soluble compounds are preferable for intravenous use but if necessary menadione may be given in normal saline 1 mg in 10 cc of solution Menadione in corn oil may be administered intramuscularly

In *hypoprothrombinemic states* vitamin K should be given daily since effective action will not extend much beyond twenty four hours In jaundiced patients and in patients with lesions of the intestinal tract affecting absorption vitamin K should be given routinely preoperatively and continued postoperatively until recovery is complete regardless of whether a bleeding tendency has been demonstrated The effectiveness of therapy is followed by daily determinations of prothrombin activity of the blood In the presence of severe liver disease the administration of vitamin K in daily doses of 10 mg or more may be without effect

Vitamin K is relatively nontoxic and

* See also Chapter 13

doses as large as 20–30 mg daily for several weeks have been used without untoward reactions. Larger amounts have resulted in vomiting, albuminuria and porphyrinuria.

In the treatment of hypoprothrombinemia following "dicumarol" therapy, vitamin K_1 or vitamin K_1 oxide has been found to reduce prothrombin time when given in a dose of 500–1000 mg intravenously. Other vitamin K preparations appear to be less effective and may be toxic in doses greater than 250 mg. Transfusion—to provide prothrombin for immediate use—is the therapy of choice if bleeding has occurred.

TABLE 48 *Cont nued*

D sease	*Th apeu c d t*	*Rat onale*
Hypoglycem a (funct onal)	H gh pro e n starchy carbohydrates low sugar	Prov de slowly a a lable glucose
Hypoparathyro dism	H gh calc um low phosphorus	Low blood calc um no mal or h gh blood phosphorus
Jaund ce obstruct e	Low fat h gh prote n carbohyd ate v a m n K v tam n A (aqueous) chol ne	Impa ed fat abso pt on of en l ver damage
Neoplas a	Attract ve suppor ve d et adequa e *calor* es B v tam *ns*	Anorexia defic ency n B am ns common
Nephr is		
Acu e glomerular	Low prote n sodium	Decrease work of k dney de crease wa er reten on
Nephros s	H gh prote n low salt	Replace prote n loss decrease water reten ion
Obes ty	*Low calor es v tam n supplements f* calor es below 000	We ght reduct on
Pancreat is	Caut ous beg nn ng (warm water tea) low fat h gh prote n and carbohy drate no meat fa s or alcohol half protein by hydrolysa e fat soluble v tam ns	Impa red d gest on and absorp t on of fat and p o e n
Pellagra	H gh prote n and B v tam ns n ac n	Tryptophan and n ac n defic ency
Pep c ulcer	Bland non ac d st mulat ng A o d v ta m n defic ency esp asco b c ac d	D e often low n v tam ns
Polycy hem a e a	Low ron of en high calor e	Metabo sm may be ele ated
R ckets	H gh ca c um and phospho us m lk V tam n D	Defic ency v tam n D promo e *calc um* absorp on bone for ma on
R boflavin defic ency	H gh B v am ns r bofla n	D eta y defi ency r bofla n
Scurvy	H gh v tam n asco b c ac d	V am n C defic ency
Steato rhea	H gh calor es protein carbohydra e low fat sugar fat soluble amins *calc* um	Rep ace lost nut en s fat glu cose and calc um absorpt on poor
Sprue Celiac syndrome	As n s eatorrhea s rawberr es bananas fol c ac d vitamin B ₂	Fol c ac d and perhaps am n B ₂ def c ency
Tetany	H gh calc um v tam n D calc um salts	Low blood calc um
Urem a	L m tat on of prote n adequa e calo es	Azotem a anorex a
Urol thias s	Low calcium no o erdosage tam n D perhaps v am n A	Avo d metabol c cond t ons fa o ng stone fo mat on
Ur c acid	Low pur ne sod um b carbonate a t mes	
Cyst ne	Alkal ne ash d et	
Oxalate	Low oxalate d et	
Calc um phosphate	Ac d ash d et (unless nfect on p esent)	
V am n A defi iency	H gh v am n A	V tam n A defic ency

When the adipose tissue is lost these functions often return to within normal limits

It is true that the overweight of the hypothyroid individual may be due to myxedema There are, however, as many thin hypothyroid individuals as there are obese ones, and contrary to traditional opinion obesity is not a specific disturbance in those individuals whose thyroid gland is underfunctioning The low basal metabolic rate often met in the obese patient is only an apparent one, if the ratio of the oxygen consumption to the body weight is recalculated in accordance with the ideal weight it will be found that the majority of these patients *will have* a normal or even an excessive rate Such a correction is warranted because the ideal weight indicates the amount of respiring body tissue while the total weight in an obese individual includes a great deal of relatively dormant tissue True endocrine obesity such as in Cushing s syndrome is rare and distinctive and has its special and specific therapy

Commonly the strain associated with a change in endocrine status, such as during puberty menopause or pregnancy may produce psychologic tensions sufficient to lead to emotional regression and overeating In these cases of course it is not an abnormal glandular condition that causes the obesity, but the strain of a change from one normal condition to another

A more subtle situation may exist during the premenstrual period when women may develop strong craving for food especially sweets Another situation involving the endocrine glands is the unsuspected increase in appetite from administered thyroid with a consequent gain in weight

It is of course not to be inferred that the glandular status of the overweight individual should be tacitly assumed to be normal As a matter of fact a properly instituted course of weight reduction involves the utilization of considerable knowledge of internal medicine, gynecology, endocrinology, psychology, and occasionally surgery is adjunctive treatments

PSYCHOLOGIC FACTORS

Ostensibly the treatment of obesity is the simple one of adjusting the caloric level to below that expended until the ideal weight is reached and then instituting a permanent balance between the two The simplicity of the end desired is however not duplicated in the simplicity of the means to that end the achievement and retention of the obese patient s cooperation

This is not the place for a detailed consideration of the psychologic implications of overeating Attention should be drawn however, to the identification of eating with the basic drive for self preservation and the supreme importance of this identification in the newborn where it forms almost the sole expression of the libido Later the gratification of this basic need becomes associated with the emotional attachment to the mother, and is, therefore made a part of the earliest experiences of satisfactory interpersonal relations

The association of food with love is a strong force in all societies Any failure to achieve emotional maturity, or any regression to the oral stage of sexuality will result in the patient seeking gratification in eating or in some symbolic replica such as nail biting or excessive smoking Because this is an immature—a neurotic—activity gratification is never fully experienced and the vicious cycle of "compulsive eating may be created Self pity is a prominent causation of overeating where the individual condoles himself with the feeling that "at any rate, he will be good to himself if the world will not Most people however regress to the level of oral gratification only temporarily and under conditions of emotional strain Such habits during crises or periods of tension as increased gum chewing and the other symbolic forms

33. Obesity

S CHARLES FREED

IN SEVERAL ways the attitude of the physician towards obesity has undergone change in the past few years Perhaps the most important of these changes has been the increasing realization of the effects of obesity on the health of the patient Statistical studies initiated by the life insurance companies have established that every excess pound over the ideal weight has damaging effects on the chances of longevity In addition the added work entailed by this load of unfunctional weight contributes to the susceptibility to many diseases Patients who are overweight are far more likely to suffer from arteriosclerosis hypertension, myocardial disease, hypertrophic arthritis and other degenerative disorders In addition weight reduction provides an inestimable amount of benefit of an esthetic and emotional nature, not only to the patient but also to his family The correction of obesity is no longer only cosmetic it has become one of the most important parts of preventive medicine

The second important change in attitude lies in the realization of the paradox that whereas the physiologic etiology is simpler than has hitherto been accepted the psychologic forces leading to the excessive consumption of food have their roots deep in the total personality of the patient and do not form the simple conflict of will power versus self indulgence that led to the traditional impatience and harshness shown by the physician

Etiology

IT WAS partly because of this over simplified attitude towards the motivation of the excessive eater that the multitude of excuses for refractory obesity became accepted Prolonged and repeated researches have however, demonstrated conclusively that obesity in the vast majority of cases is the result of an imbalance between caloric intake and expenditure—of the patient eating more than he needs to maintain his weight and health Involvement of the glands usually contributes only secondary or indirect influence and is not primarily responsible for the overweight Laboratory investigations of changes in the metabolic or glandular status of obese individuals have proved these changes to be the result of overweight and not the cause of it

a long illness not balanced by an equally restricted intake of food, and may consequently give rise to an accumulation of unused nourishment that turns to fat, but by far the most important factors are the emotional tensions induced by the organic illness, such as anxiety and boredom In children with overanxious parents, since the administration of excess food relieves the parents worries over the child s illness, sickness is very apt to lead to obesity Physicians are often confronted with obese patients who were sickly children or premature babies

Ideal and Excess Weight

IN THE preceding discussion the status of obesity has gone without definition This is to a certain extent inevitable—there is no precise line separating the normal from the abnormal accumulation of fatty tissue Generally the physician will be confronted with three types of patient, the reduction *of whose weight he must undertake the* obviously obese individual who desires—often for purely cosmetic reasons—to lose weight the patient who while not fat by any usual standards needs to lose weight in order to continue successfully with his career, and the patient whose obesity, while not marked or a cause of social discomfort, is contraindicated because of concurrent disease or age *

In the first two cases *the question of definition* does not arise—in one the patient is too far past *any dividing* line between obesity and ideal weight for the problem to need *consideration,* in the second the desire for weight reduction is dictated by *nonmedical reasons*—and in both cases the decision to be made is the effect of the weight reduction upon the general health of the patient In the third case two general principles may be of use The first is that through youth and early maturity it is better to be slightly overweight than slightly underweight (as determined by the average weights of comparable sex and age) and that in later maturity and after the reverse is true *The second is that for the* second half of life the ideal weight is that which was ideal at the age of twenty five

All patients *in middle age or later* who weigh more than they should have at twenty five are obese The degree of this obesity and the reasons for it will determine the clinical importance of the condition

The use of tables of ideal weight is often impractical since they do not consider the skeletal architecture of the individual or the distribution of fat tissue Furthermore, tables in use a few years ago are inaccurate due to the general improvement in body build in the past decade The physician's clinical acumen is *most valuable in deciding* the proper weight of a patient

* See also Chapters 15 and 31

of eating mentioned above have the same significance—but not the same unfortunate metabolic effects—as overeating

It is partly because of the unconscious significance of oral gratification that eating plays such a large role in the attainment of social status The ability to offer good food and plenty of it is of prime importance not only in the exercise of hospitality but also in the manipulation of business or political deals Other aspects of the social or emotional drives towards overindulgence are the influence of economic deprivation in childhood or employment in a business associated with food

It must not be inferred from this that all obese patients are candidates for the psychiatrist However it must be remembered that the doctor who undertakes to treat a fat patient is concerned with the patient s eating habits and not—at any rate primarily—with his fat cells While in the majority of cases these habits are not of major pathologic significance the physician should know what they do signify and be prepared to help the patient by more sympathetic and efficient means than exhortation and ridicule to attain the cooperation that both desire

NONPSYCHOLOGIC FACTORS

In spite of the paucity of evidence that the biochemical processes in adipose patients are abnormal many clinicians still feel that there is a biologic factor that distinguishes some obese patients It is to this clinical impression that the writer of this chapter must revert for the contention that certain individuals do possess a characteristic which allows a relatively easy gain in weight apparently uninfluenced by the psychologic factors we have mentioned and which may be transmitted to some of the offspring There are many individuals who gain weight on an intake of food which will only maintain the weight of many normal persons or even result in a loss of weight in others Weight reduction in these patients is as a rule rather slow if the usual reduction diet is employed Moderate indiscretions immediately cause a halt in the loss of weight It would appear that the caloric expenditure of certain individuals is under ordinary conditions definitely less than others who perform the same amount of work The reasons for this lower energy output may be due to certain personality traits such as the ability to relax completely, to remain motionless for longer periods of time and probably to certain physical characteristics There has been observed in a large proportion of these individuals slow pulse rates low blood pressure, sluggish reflexes and an inability to express emotions by skeletomuscular reactions These manifestations are not specific, of course, but on observing large numbers of heavy people this constellation of intrinsic and extrinsic factors has been found to be more common in those whose weight is easily increased than in those who maintain average weight It has also been noted that these individuals descend from long lived ancestors It is quite possible therefore that this tendency to gain is inherited and it may be explained by exceptional metabolic efficiency rather than abnormal biochemical reactions

Other somatic factors may occasionally be of consequence in the etiology of obesity Excessive weight is often dramatically developed when the nerve center in the hypothalamus controlling the consumption of food is injured The same can occur when the inhibitory impulses from the cortex are eliminated due to brain damage Tumors of the brain may cause obesity by encroaching upon the hunger center of the hypothalamus with the possible production of true Froehlich s syndrome

Accidents operations and somatic disorders are often responsible for gains in weight This is in part due to inactivity of

who are thin or ideally weighted Quite commonly encountered are those who have the constitutional type of overweight resulting from eating amounts of food which are not excessive for the average person These heavier individuals can hardly be accused of having a more neurotic appetite than the more fortunate thinner persons Until there is evidence that the majority of these cases require fundamental psychotherapy there is justification for using the admittedly superficial but effective methods now available to aid the patient in his effort to lose weight Where there is relative emotional stability it may suffice to use the milder forms of diet drugs and psychotherapy at the disposal of most doctors Where there are overpowering compulsions for eating and other symptoms of psychoneurosis one may then call upon psychiatrists for aid

Cooperation of the Patient

One of the essential factors in the successful treatment of the overweight patient is understanding which will secure cooperation between the patient and the physician *The physician must have a sincere and* sympathetic attitude toward the patient s condition He must be aware that obesity *is* a serious and life shortening disturbance and therefore adopt the same attitude toward *it that* he does toward other problems in internal medicine such as hypertension *arthritis and gastrointestinal* ulcers which may also have a psychosomatic basis

The Patient s Self Respect The physician must realize that most overweight *patients* are unhappy and secretly detest themselves despite their outward cheer for being *unable to* maintain themselves on a proper dietary regimen A contemptuous brusque *or* belligerent attitude on the part of the doctor aggravates in the patient his self-dislike and feelings of guilt and does no appreciable good except perhaps for a short time A facetious attitude also is unwarranted since friends or relatives already have undoubtedly heaped considerable ridicule upon the patient A too strict attitude with rigid discipline is also to be avoided since temptations to the overweight patient are many and strong even the most cooperative one may under certain conditions be induced to break his diet routine If this is handled too sternly or unsympathetically it may establish intense guilt feelings and a hesitancy on the part of the patient to confide in the physician about some of these situations the treatment thus being impaired or terminated

Initial Interview The physician should explain when he first sees the patient that he is not a policeman that he can only help him over a course which at best may be difficult that the patient requires help and that in order to aid him the physician should be informed of everything of significance that the patient does or thinks concerning not only diets but also family and economic situations The physician must then explain exactly what obesity will do to the patient how it will affect his health and *his self esteem The incentives for* weight reduction are explained in terms which will have greatest appeal to the individual for example to a woman the cosmetic effect of which she is undoubtedly aware is stressed Likewise her social life will be expanded unmeasurably with loss *of self consciousness With men* emphasis on health and prevention of degenerative diseases may have more appeal If the patient is intelligent the mechanisms and dynamics of eating can be simply *outlined* it being explained that eating is an urge which is part of the psychology *of all people* but that *for one reason or another it* is intensified in those individuals who have become overweight Likewise it should be explained to these patients that *they* are not to be considered shameful creatures with weak will power since this is a vague

Treatment

ONLY a person who feels well can reduce properly, and the treatment of an obese person requires the investigation and analysis indicated for any problem in internal medicine. Emphasis should be placed, however, on the emotional background. This requires questioning concerning the food habits from infancy, economic and social environment, and relations with other members of the family, especially parents, siblings and husband or wife. In addition, knowledge of the position of the patient in the family may be of value: an eldest child —perhaps because of the tendency to regress to the oral stage upon the birth of a younger child—is more likely to be obese than others; an only child is also prone to be heavy since he has a more difficult path to maturity.

Patients should be questioned concerning their own reasons for overindulgence. It is surprising to learn the varied explanations for the act. Fatigue, irritability, boredom, anxiety, hostility, self-punishment, dissatisfaction and depression are among the causes mentioned.

Inquiries should be made of the type of food preferred. Some individuals have no special food habits, while others may crave sweets, starches or fatty foods. Education of the patient to use the proper diet will depend to a certain extent on his knowledge of the richness of the foods which he eats. Questions should also be asked regarding the relation of meals to occupation, environment and social habits. Many obese individuals will commonly omit breakfast, eat a light lunch, and in the evening indulge in large amounts of food. Food habits also may be different on week ends or during vacations.

A complete physical examination should not be neglected. Any other organic or functional disorder should be investigated fully and treated accordingly.

PSYCHOTHERAPY

Since restraining the intake of food to an appropriate level depends on the solution of an emotional problem, one may be inclined to assume, resignedly, that all cases of overweight are psychiatric problems and should be treated by psychiatrists or those with appropriate training. This feeling may be strengthened by the realization that the emotional desires toward eating have their origin deep in the unconscious, and that only a psychiatric approach that can alter these deep-rooted urges provides lasting effects. Practically, however, the financial and economic aspects will permit only a minute percentage of patients to avail themselves of such therapy. Even were the patients ready and willing to enter upon such an expensive and time-consuming project, one may be permitted reasonable doubt that even complete psychoanalysis would result in sufficiently radical and long-lasting alteration of these instinctual drives to compensate for the effort and money required for such therapy. Furthermore, it is open to question whether obesity per se is an indication for psychoanalysis. There is no doubt that where a patient is obviously psychoneurotic, one of the manifestations being an abnormal craving for food, all attempts should be made to encourage the patient to seek the appropriate psychotherapy; but in considering the majority of overweight cases one hesitates to label the difficulty in restraining from food as a neurotic drive even though one believes it is an emotional problem.

In this regard, the intensity of the desire for satiation by eating in some obese people may not be any greater than that of those

health, or once started upon dieting he would become ill At the proper time it may be explained to these individuals that these excuses merely serve as alibis for their failure to lose weight Naturally, if the doctor shows an attitude of tolerance and sympathy patients will not so readily develop the intense guilt feelings that call for such rationalizations In fact, the physician will be impressed by the gratitude displayed by these patients when they learn that they are to be helped not punished They will be far more loyal and more apt to persevere to a successful conclusion of the treatment

Status of the Physician In addition to this the importance of the prestige of the physician in the treatment of obesity must be considered Upon this will depend to a great extent the readiness with which a dietary regimen is accepted and the tenacity with which it is followed If for any reason the diet is ignored and the patient is led to feel unduly guilty or ashamed the useful dependency upon the doctor will be broken by the patient s criticism of his physician to his friends and relations in an effort to save face This will not only probably terminate the patient s treatment but also limit the physician s future usefulness to any who have listened to his patient s rationalizations

The doctor must also be on guard for the diet enthusiast who limits the food intake to coffee and fruit juices After some weeks a nervous and weak condition develops and the physician may receive the blame not only from the patient but also from his friends

For these reasons then it is best to begin treatment with each new patient by offering a frank honest appraisal of the problem Physicians with a minimal of psychiatric training can give great aid to their patients by adopting this attitude Patients should be warned that at a later date any increase in psychic tension or any unusual difficulties in domestic economic, or social spheres may upset their routine and progress in the reduction of weight or initiate an increase It may be helpful to warn the patient of this possibility but often it does not prevent the complication Certainly it will not correct the underlying emotional dynamics It will, however, in many cases prevent overwhelming discouragement or a breakdown in the morale of the patient which might result in discontinuance of treatment Patients will be more readily available for further treatment if the feelings of guilt and shame are removed and they know that these situations are not abnormal or a sign of weakness of character in the usual sense

It has been demonstrated that obese individuals can be subjected to hypnosis and will follow posthypnotic suggestions to refrain from eating Such influences are effective for some time after the hypnotic session but there are insufficient data concerning the ultimate results of such treatment It may be that other psychic disturbances may replace the inhibited emotional urge for oral gratification This form of treatment may be superior to the common weight reduction methods but the absence of psychic upsets following hypnotherapy has not been sufficiently established at the present time to recommend it in most cases It may be useful in special cases where prompt weight reduction is urgent in certain individuals with strong eating compulsions

Frequency of Office Visits

It is well to see patients fairly often perhaps once weekly for three or four weeks and then less frequently perhaps every two or three weeks depending on the progress and personality of the individual Too frequent visits are excessively expensive and may be discouraging to the patient On the other hand infrequent visits will weaken the patient s dependency on the doctor and will permit too many indis

term others who may display will power in consuming food find it just as difficult to give up smoking, drinking, or gambling

These patients should not be pampered or treated as children, however, nor should their slightest whims or desires for food be appeased Often one must be firm, and at certain points force the patient to recognize that he will have to choose between good health and the other benefits of weight reduction, and the pleasure of eating He should then be told that eating for pleasure is dangerous to his welfare, and that good health demands that he renounce these pleasures and choose more mature ones

Food habits cultivated over the years should be changed gradually as the normal catabolism diminishes with increasing age It is not essential to fill the stomach until a sense of satisfaction is obtained The principal function of food is to furnish energy and not oral gratification

Friends and Relatives Explanations also should be given of the attitude of friends and relatives Often the influence of these individuals causes a great deal of harm They may have ridiculed for years the overweight patient and issued stern edicts and advice or have pleaded at length for the patient to restrict his diet Nevertheless when patients start losing weight the same individuals become alarmed and issue dire warnings of the danger of ill health Dieting and the problem of overweight is probably one of the most discussed topics at social functions and distorted stories regarding the experiences of friends who have lost weight make the rounds and become more distorted with each telling The tragedy of "dinitrophenol is of course responsible for much of the fear observed in some people who are on diets, especially when medication has been prescribed Individuals who are overdosed with thyroid are also responsible for many sordid tales attributed to weight reduction The patient should be told that weight reduction under a doctor s care is harmless and beneficial, and that his friends comments should be ignored

Overprotection Mothers will very often express great concern regarding the adipose condition of their children Many of these mothers, however, find themselves unable to deprive their children of food once the reduction therapy is started, and they may unconsciously keep sweets and other tasty foods of high calorie content about the house to tempt the children, or they will place the children at a disadvantage by serving rich food to all other members of the family

Such an attitude is related to the symbolism that food is love, and that feeling on the part of the mother that she must constantly demonstrate her love to the child by providing him with food even though it is harmful It should be explained to such a mother that if she truly loves her child she should be concerned with the child s future welfare in the world, that the child s happiness and health is intimately associated with a normal body and that she is the guilty party if harm occurs from excessive food intake The treatment of children under 13 or 14 years is quite unsatisfactory as a rule and is best handled by educating the mother The child is usually unappreciative of the benefits of weight reduction and it is difficult to furnish an incentive The physician has a relatively small basis for rapport to exert any psychological pressure so that cooperation is difficult to achieve Formal psychotherapy is however, most effective in the younger patient

Excuses for Obesity Individuals who attribute their overeating to a glandular disorder should be told that even were that the cause nevertheless they would have to adhere to a reduction diet Frequent rationalizations of a patient's inability to stay on a diet are that obesity runs in the family that some doctor told him not to lose weight because of his

TABLE 19 TYPICAL REDUCING DIET

BREAKFAST

Choice of
1 Orange or orange juice
1 Tomato juice (fruit juice glass)
½ Grapefruit with one scant teaspoonful of sugar
½ Cantaloupe

Choice of
1 Egg (may be boiled or poached)
2 Strips bacon

Choice of
1 Thin slice of bread (may be toasted)
⅓ Cup any cereal (with milk)
1 Small roll

Choice of
1 Glass of (skimmed) milk
Tea or coffee as desired

LUNCH[1]

Salad or sandwich beverage fruit or jello

EVENING MEAL[1]

Clear soup and vegetables
Large serving of salad composed of any of the following

Head lettuce	String beans	Beets
Tomatoes	Cabbage	Celery
	Carrots	Endive

1 Thin slice of bread
4 oz of one of the following

Lean beef	Lean veal	Chicken or turkey
Lean roast	Lean lamb	Fish
Steak	Hamburger	Eggs (2)
Ham	Liver	Cottage cheese

2 Servings of any of the following

Brussels sprouts	String beans	Radishes
Cabbage	Cauliflower	Okra
Spinach	Turnips	Peas
Beets	Squash	Asparagus
Carrots	Sauerkraut	

Choice of fruit jello or sherbet
Beverage

SAMPLE MENUS

Breakfast	*Lunch*	*Dinner*
I	I	I
Fruit 1 Slice toast 1 Teaspoonsful butter 2 Strips crisp bacon Coffee or tea[2]	Soup (clear vegetable) 1 Slice bread 1 Teaspoonful butter Salad 1 Glass skimmed milk or butter milk	Meat (4 ounces lean) 1 Vegetable Salad Fruit
II	II	II
ruit Slice toast Teaspoonful butter Egg poached ffee or tea[2]	Fish (4 ounces) 1 Slice bread 1 Teaspoonful butter Salad Fruit	Meat 2 Vegetables Salad 1 Glass skimmed milk or butter milk Fruit

cretions before corrective habit formation can be developed

During these office visits the physician questions the patient as to his well being or fatigue, any reaction to medical treat ment, the ease of dieting and obstacles which may be present that interfere with a proper routine It cannot be overempha sized that a patient must feel well for proper weight reduction This includes the *elimination of emotional tensions so that* he should be able to restrict his diet with as little effort as possible As stated before the reduction of nervousness includes the treatment of any coincidental medical dis turbances which may exist This also in volves a thorough education of the patient *in the benefits of dieting an unconscious* anxiety may arise when weight is lost since the weight gain was originally a means to combat an inner anxiety Constant reassur ance may be advisable as well as encour agement to continue in the face of criticisms and distortions of facts arising from friends and relatives and even unfor tunately, some unenlightened physicians

Relapses There are some cases in which after an initially satisfactory response the patient s overweight becomes refractory particularly in the constitutional cases Al though in most cases it is impracticable to suggest psychotherapy would at this stage provide great benefit even where some weight reduction has already occurred Doubts concerning this partially successful treatment can usually be dispelled by the realization that the improvement in health is more than sufficient compensation for the financial expenditure even if a compar ison is not made with the possible expendi ture required in the treatment of such diseases as hypertension arthritis and other refractory conditions that may be caused by the continuation of obesity

Hospitalization It is of considerable importance to treat the patient in his own environment Weight reduction in an insti tution or hospital is simple since emotional factors of the home and business world are practically eliminated The patient thus being sheltered from unpleasant stimuli and responsibilities undoubtedly will do well, but upon returning to his home fre quently will relapse into his old eating habits if his attitudes have not been altered or his tensions alleviated

DIET THERAPY

Caloric Requirement

It is logical that in order to cause reduc tion of weight, the total caloric content of the reduction diet should be below that which the patient requires to maintain weight In determining the caloric require *ment, one must bear in mind the constitu* tional factors (which can be recognized from the history of the individual s food habits) and the occupation of the individ ual Hard physical labor will permit a greater intake of calories than a sedentary occupation without resultant gain in weight Tall individuals with more surface area to maintain at body temperature re quire more food than short individuals The age of the patient is also of importance in estimating the required caloric intake The total metabolism decreases as age in creases so that the reduction rate of an individual at 20 years on a stated diet will be much more rapid than the same indi vidual five or ten years later A child at puberty and in the active state of growth requires special consideration because of the need for vitamins minerals, proteins *and other necessary food elements*

There is, therefore considerable varia tion in the caloric content of any one re duction diet It is suggested that a basic diet of approximately 1000 calories be pre scribed for the average patient, for example, a moderately overweight housewife 35 years of age This diet can be modified by either larger or smaller portions of the included

majority of patients either have no extra time to prepare their own foods, or eat in restaurants, and the diet should be adapted to meet these requirements The author of this chapter does not believe that the patient should be required to weigh out food, to consult books as to the caloric content of each item, or that it is necessary to present the patient with a diet which requires a statistician to understand Diets with cross references to various groups of food items which require constant referrals to tables may be sufficient reason for certain impulsive individuals to avoid the routine altogether It is true that some patients may actually enjoy this type of detailed activity This may give them an outlet from their boredom or feeling of insecurity so that some of their inner tension is expended in the labors of preparing a complicated diet, but even in these cases such efforts soon become tedious

The diet should contain certain basic requirements of food elements There is little danger of nutritional deficiencies however, if the diet contains several portions of fruits and vegetables and four to six ounces of natural proteins from eggs, fish, meat cheese, or milk The diet should then be made palatable by prescribing a variety of choices of the various substitute foods A basic diet can thus be prepared, to be modified in accordance with the estimated requirements of the patient If after a period of two or three weeks this adapted diet is not producing sufficient weight loss, and the physician is convinced that the patient is adhering to the diet further modifications may be made If weight loss is too rapid, patients may be given additional food The diet shown in Table 49 has been found to meet the above requirements

These diets should contain at least 1 Gm of protein per Kg ideal weight Children may have more protein foods up to 2 Gm per Kg This diet also contains sufficient carbohydrate to provide adequate quick energy and to prevent ketosis, and satisfy vitamin and mineral requirements It is suggested, however, that with children a multivitamin supplement be added daily to insure proper growth and development Some adults claim they feel better with supplementary vitamins

This diet may be low in calcium if milk is not taken by adults Prescription of a high potency vitamin D capsule to be taken once a week will permit sufficient mobilization of calcium from the food to prevent signs of calcium deficiency which may be indicated by complaints of brittle nails or muscle cramps

Patients who are suffering from certain bodily disorders may require more radical alterations in the diet Thus, hypertensive individuals may be given diets with low sodium content and perhaps a minimal amount of protein * Those with peptic ulcers may require frequent feedings and the elimination of irritating vegetables The patient with ulcerative or mucous colitis cannot ingest most vegetables of the low carbohydrate group Often the patient recognizes those foods which are harmful and can thus easily avoid them The diet described above is ideal for overweight diabetics and those patients with gallbladder disease Certain serious illnesses such as heart failure which require reduction of excess weight are relatively easy to handle since the emotional aspects of eating are readily combated by the patient's acute realization of the nearness of death †

Sugar and Alcohol It is of great importance to omit from the diet foods with large amounts of sugar Not only is the caloric content of these foods an obstacle to reduction, but there is a body reaction to sugar which leads to an increased desire for more sugar This physiologic action has been demonstrated in laboratory animals an injection of glucose is followed by a rise

* See Chapter 15
† See Chapter 10

TABLE 49 (*Continued*)

Breakfast	*Lunch*	*Dinner*
III	III	III
Fruit Boston brown bread 1 Scrambled egg Coffee or tea[2]	Soup Salad Meat Fruit 1 Glass skimmed milk or butter milk	Meat 1 Vegetable Salad Fruit 1 Lady finger Coffee or tea[2]
IV	IV	IV
Fruit 1 Boiled egg 1 Slice toast 1 Teaspoonful butter Coffee or tea[2]	Soup Sandwich 1 Medium baked apple	Meat 2 Vegetables Salad Fruit Coffee or tea[2]
V	V	V
Fruit Cereal (with milk) Coffee or tea[2]	Soup Cottage cheese Sliced tomato on lettuce Fruit gelatin	Canape Meat 1 Vegetable 1 Cup custard
VI	VI	VI
Fruit 1 Bran muffin 1 Teaspoonful butter Coffee or tea[2]	Omelet Salad 1 Slice bread 1 Teaspoonful butter 1 Glass skimmed milk or butter milk	Tomato juice Fish 2 Vegetables 1 Cup junket
VII	VII	VII
Fruit 1 Soft boiled egg 1 Slice toast Coffee or tea[2]	Soup Meat Salad 1 Glass skimmed milk or butter milk	Meat 2 Vegetables 1 Teaspoonful butter for vege tables 1/2 Cup fruit salad 1 Graham cracker

[1] Do not use fat in the preparation of food Remove all visible fat from meat Mayonnaise may be made of mineral oil (½ pint) beaten into 1 egg yolk and 1 tablespoonful of vinegar and seasoned with salt pepper mustard and paprika Use as little salt as possible

[2] With cream and sugar if desired

foods Other foods may be included in cases where the caloric intake is to be increased or the basic diet can be trimmed further if the calorie intake is to be reduced in accordance with the various factors already discussed

The Reducing Diet

The diet should have the following features It should have a sufficient deficit in calories to cause appreciable but not too great a weight loss—on the average between 1½ and 3 pounds a week—although in very large individuals a more rapid weight loss is not undesirable for several weeks it should be palatable so that patients will enjoy eating whatever they are permitted in the diet, it should have considerable variety to avoid boredom or weariness in following the routine, and the food products should be easily available Many published diets indicate food and dishes that are available to only the few patients who have a dietitian or cook in their home, or who can spend considerable effort and time in the preparation of foods The

maintain a satisfactory weight and can thus form the basis of a normal eating routine If weight has been lost rapidly additional food may be given for the purpose of obtaining and maintaining the desired weight It is well to instruct the patient to return to the doctor if he gains over five pounds of weight and feels he cannot prevent further gain

DRUG THERAPY

Many patients require only simple advice and education concerning the caloric content of foods and proper food habits and placement on a restricted diet to effect weight loss However most patients who approach a physician to lose weight require additional help as they have already made efforts to restrict their diet and have failed Fortunately there are available a number of drugs which are of considerable benefit in treating obese patients and which make the routine of dieting less unbearable Of course medicaments are used to combat other existing bodily or mental disturbance if drug therapy is indicated

Amphetamines

The basic drugs used in individuals who require help to control their obesity problem are the amphetamines the two most important being racemic amphetamine and dextro amphetamine These compounds in the proper dosage can reduce the desire for food and combat the compulsion for eating The racemic form is commonly administered in dosages of 5 mg three times a day, thirty to sixty minutes before each meal The dextro form is administered similarly in dosages of 2 5 mg There will be some individuals who will require larger dosage of these drugs the amount may then be doubled at those times during the day when the patient s appetite is apt to be more intense The author has recently demonstrated that a combination of 5 mg racemic and 5 mg dextro amphetamine administered three times daily is unusually effective in curbing appetite with a minimum of side-effects in resistant patients Only rarely do reasonable amounts of these drugs fail to curb appetite then it probably occurs in those whose compulsion for eating is overpowering and who may require a form of deep psychotherapy or in patients who are under a severe emotional strain Likewise the effectiveness of these drugs is impaired in women undergoing premenstrual tension

The mechanism of the amphetamine action is probably threefold First it quiets the peristaltic action of the stomach thus lessening hunger sensations and also delaying the emptying time of the stomach so that this organ remains fuller for a longer period of time Second it probably has a central nervous system action in lowering the threshold to satiation of food especially in certain individuals who may be relatively unaware of the filling of the stomach and who only become sated when the stomach is distended far more than that required for normal individuals to register an equal sensation Finally it produces a feeling of well being thus combating fatigue and irritability which is quite common when food is restricted and encouraging patients to expend appreciably more energy in activities

Such an approach eliminates some of the more common causes for breaking the diet This aid in reducing is of tremendous benefit to the morale of patients since many of them experience a seemingly hopeless inability to withstand the temptation of food By this means not only does the patient lose weight without exerting his so-called will power, but he is also encouraged to continue dieting for prolonged periods of time with this new confidence in his ability to stay on a diet

Limitations of Drug Therapy When a physician gives a drug such as the amphetamines he should realize that the

in blood sugar and then a drop below the normal blood sugar level This mild hypo glycemia results in an automatic demand for more sugar Abstinence from this food will allow a more stable blood sugar level

Likewise, alcohol has a multiple effect The caloric content of alcohol is equal to that of sugar and in large amounts will prevent satisfactory loss of weight Further more it will inhibit the cortical centers and release the emotions for oral gratifica tion as well as stimulating gastric activity, thereby increasing hunger sensations How ever, an occasional drink at a social func tion is permissible

Water Retention

Dieting may be sufficient to cause weight reduction to the ideal weight and to per mit a fairly permanent maintenance of this ideal weight Often, however, a patient will remain faithfully on a diet for a number of weeks without an appreciable weight loss or a plateau in the weight curve may be established after he has begun to lose weight This is most discouraging to the patient and to the physician, and it may continue to be discouraging to the patient even when it is explained that he possibly is only retaining fluid, which has been demonstrated adequately to be the case in many instances Apparently adipose tissue may have a tenacity for water up to a cer tain point, then the water is released rather rapidly so that there may be a dramatic weight loss if the patient continues on his routine The total weight loss will then ap proximate that predicted by the caloric deficit

In women who are menstruating fluid retention is especially prominent during the premenstrual period These individuals will often volunteer the statement that they feel bloated Steroids of the ovaries have a sodium retaining effect, and since they are at their highest peak in the premenstrual phase this accounts for the added water in the tissue at this time, and the cessation of weight loss By providing ammonium chloride or reducing the salt content of foods, this obstacle to morale may be obviated

Side Effects of Weight Loss

One of the more common reasons for patients discontinuing their diet routine is the sensation of weakness or irritability which may develop during weight loss Such symptoms may be the result of a low concentration of blood sugar and may be effectively combated by permitting patients to have some sort of refreshment between meals such as coffee, tea, fruit juices, or other beverages of this nature Occasionally a menstrual cycle will be either shortened or lengthened coincidental with weight loss Simple reassurance that this is of minor importance usually satisfies the pa tient It may also be explained that often weight loss results in improvement of ovarian function so that abnormalities of menstruation habitual abortion or steril ity may actually be corrected by the reduc tion of weight. Constipation is a frequent complication of dieting simply because of the relatively low carbohydrate content of the diet and the increase in proportion of cellulose containing foods This constipa tion may be a brief one in patients who normally have regular bowel habits Ap parently the intestinal flora is changed with the alteration in diet to adjust to the new situation The condition is more se vere in those with a previous tendency to constipation, and it may require for some time the use of some form of mineral oil or milk of magnesia in moderate doses Pa tients with chronic constipation are rather difficult to treat at times, but after a vary ing period their former bowel habits are restored

Maintenance Diet After the patient has finished the course of treatment, the diet described in this chapter will often

trinsic organ stimuli such as the feeling of fullness of the stomach (vagotonic?) The dextro form is best administered to the high strung individual, who is aware of intrinsic organ stimuli with a tendency to palpitation and dysmenorrhea (sympathicotonic?) and a sensitivity to the action of drugs

Hypertension and Amphetamines The occurrence of hypertension in the obese individual is of special importance There have been warnings that the amphetamines are contraindicated where hypertension is found Since these individuals have a special need for weight reduction it would *be unfortunate if they were deprived of* the benefit of these drugs There is considerable evidence however, that a sedative such as phenobarbital 15–30 mg three times each day administered with the amphetamine may reduce the hypertension in a satisfactory manner

Proprietary Drugs

There are in common use for the treatment of overweight various preparations containing amphetamine products and a variety of other drugs in the same tablet or treatment schedule These are usually marketed in colored tablets which are to be taken at certain times of the day Thus a certain color tablet taken in the morning will contain 5–10 mg of amphetamine, atropine, and a laxative such as cascara sagrada Another colored tablet taken at noon will contain in addition to these ingredients usually 60 mg of thyroid The evening tablet contains 15–30 mg phenobarbital instead of thyroid There are slight differences in the formulas adopted by different drug manufacturers It is obvious that such shotgun preparations are unscientific Undoubtedly many patients will lose weight with this type of therapy, but as is to be expected this loss of weight is quite transitory As mentioned earlier, using such medication without other forms of therapy does not allow the patient to gain insight into his disorder or to make any corrections in his behavior or attitudes When tolerance has been acquired or therapy terminated, these individuals are likely to regain their weight

An appreciable number of patients will have an idiosyncrasy to one or more of the ingredients Some patients develop diarrhea due to irritation of the bowel from constant use of the laxative drug others are intolerant to thyroid and exhibit nervous reactions, while some individuals cannot use phenobarbital without an allergic reaction Furthermore, the dosage is inflexible *and the dosage of an ingredient cannot be* properly modified to suit the individual requirements of the patient without other ingredients being increased thereby inviting toxic reactions As in all other forms of shotgun medicine, such mixtures should be avoided, and only those drugs administered for which there is a definite indication

Methamphetamine Hydrochloride and Benzocaine

Another drug which is of some value, but according to available evidence of lesser benefit, is methamphetamine hydrochloride which acts much the same as the amphetamines but with lesser effect on the appetite Ethyl aminobenzoate (benzocaine) is claimed in a few reports to have some action on curbing the appetite, but this requires further experimentation before confirmation is obtained

Thyroid Preparations

The assumption that preparations of the thyroid gland will aid in weight reduction by making up the glandular deficiency has already been discussed The pharmacologic effect of thyroid in an individual whose thyroid is functioning adequately is insignificant unless the dose approaches toxic levels The administration of thyroid to an

benefits desired from the medication are only temporary in most cases. While the patient is enjoying the results of a curbed appetite and a feeling of well being all attempts should be made to give him insight into the emotional causes of over eating as well as to eliminate the obstacles of superstition prejudice guilt, low self esteem etc If this is accomplished the dependency on drugs is diminished and, by being more able to cope with the vicis situdes of life the patient not only becomes able to manipulate his weight control but also achieves a greater degree of emotional well being

A tolerance to the amphetamines may develop after a month or more of use so the dosages may require increasing from time to time However if patients are not responding satisfactorily to a total of 30 or 40 mg daily of the racemic amphetamine it is well to consider the need for some form of psychotherapy Often however the spontaneous shrinking of the stomach from partial fillings is sufficient even with increased tolerance or cessation of therapy to control the patient s appetite

It cannot be too strongly emphasized that the amphetamines are rendered relatively ineffective unless the patient is relieved of various types of emotional tension whether it is due to a psychic disturbance or stems from an organic disorder Therefore ac companying amphetamine therapy there should be other treatment for coincidental disorders such as iron therapy when anemia xists estrogens for the menopause andro ens in clearly defined cases of male cli acteric androgens for premenstrual sion sedatives for nervousness or insom antispasmodics for various types of rointestinal or other smooth muscle n etc

ce amphetamine is of much impor n the treatment of overweight it is consider this agent for any possible l effects There has been much

publicity in the lay press in r
warning the public of damage
group of drugs This potential ha
has been vaguely described as ove
tion of the heart addiction and
upsets It is true that certain psycho
individuals receive significant men
physical stimulation from these dru
may find a constant need that lea
psychic habituation However unde
supervision of a physician there is
danger of these undesirable reactions
sicians should be able to recognize
psychoneurotic individual and withho
the drug unless psychotherapy either co
cidental with the reduction regimen o
preceding it is obtained

There are however occasional side-reactions to the racemic amphetamine which while producing no significant harm may be unpleasant to the patient These include dryness of the mouth temporary exhilaration with a sense of intoxication insomnia and constipation Most of these side reactions disappear after a few days' or weeks use of the drug The insomnia can be combated for a short time with a sedative before retiring until the patient becomes adjusted to the medication Con stipation is treated as moderately as pos sible since it too will be alleviated when the bowel becomes accustomed to the new food intake Many of these side reactions except constipation can be alleviated with the use of the dextro amphetamine if they are sufficiently intense it is well to change to the dextro form

Choice of Amphetamines Dextro am phetamine in general curbs the appetite as well as the racemic form except in certain individuals with a high threshold to sati ation or with a fairly strong compulsion for food The racemic form is indicated in this type of individual who will be found to be in general rather sluggish physically possessing a tolerance for large doses of drugs in general, and insensi

34. *Treatment in Obstetrics*

M. EDWARD DAVIS
& GEORGE J. ANDROS

Prenatal Care

PRENATAL care as it is offered by conscientious physicians to hundreds of thousands of women each year constitutes the best in American preventive medicine and is the oldest such movement of national scope As well as achieving its immediate purpose of safeguarding mother and fetus this continuing medical survey of normal women in the childbearing age serves to discover and correct many types of abnormalities unrelated to gestation While pregnancy is a physiologic process not all women who become pregnant are normal *physiologically or anatomically* The ultimate in preventive obstetrics would be the universal adoption by women of premarital and preconceptional examinations The groundwork for such a utopian situation in each community must be carried out by the local physicians

Up to the last decade the emphasis in obstetric care was placed upon management of complications Recently the swing has been back toward consideration of childbearing as a natural process Attention has been centered upon maintaining normalcy in the functions of the pregnant organism correcting minor deviations therefrom and searching out the serious abnormalities early in their development for concerted therapeutic attack The purpose is to bring the woman to labor in a physical and psychologic condition adequate to withstand the unavoidable strain

Since the medical profession has attempted to convince the laity that prenatal care begins with the date of conception the physician must do everything within his power to give the prospective patient an early first visit appointment, and at that particular time accomplish everything *within his power toward complete* evaluation of the patient and the giving of preliminary advice

FIRST VISIT

History

Following the obtaining of essential identification data concerning the patient and her husband, the physician must proceed to take a complete medical history The pregnant patient s history should be as *thorough and as painstakingly obtained* as though the patient were in for a diagnostic study at the hands of the most careful internist The outcome of the pregnancy as

obese individual will result in one of three responses He may lose weight but in doing so is subject to a rapid regain when thyroid is discontinued because the intake of food has not been controlled adequately or his food habits corrected properly, no effect is encountered although the patient may take huge amounts or there may actually be an increase in weight due to the development of a stronger appetite through the toxic effects of thyroid producing an increased nervousness and irritability In addition, long continued and uncontrolled use of thyroid may actually be harmful to the cardiac muscles the liver the nervous system, and other organs Of course, where there is clinical or laboratory evidence of thyroid deficiency the use of this drug is definitely indicated In the rare cases of myxedema weight may be lost dramatically following thyroid therapy it occurs through removal of the excessive tissue fluid deposits

The evidence that thyroid can cause combustion of fat seems quite reliable However for practical therapeutic purposes it can be safely assumed that thyroid per se in a normal individual whose diet is not altered will not cause a significant loss of weight The author of this chapter has studied approximately 300 individuals whose weight was at an equilibrium with their diet intake They were given 0 12 Gm of thyroid without any additional instructions The results of this medication on weight was statistically negligible

It is obvious that thyroid therapy should be reserved for patients with thyroid deficiencies In cases of doubt where patients have symptoms of possible thyroid deficiency or whose basal metabolism is exceptionally low, thyroid may be given as a therapeutic test If, however there is no subjective response in the patient s well being after three to four weeks the thyroid should be discontinued

MISCELLANEOUS THERAPY

The use of *physiotherapy* for weight reduction can, in general, be considered valueless However, some individuals have frequent tension headaches or backaches due to spasm of occipital and vertebral muscles which may be aggravated by the emotional strain of dieting These complaints respond dramatically to the appropriate physiotherapeutic manipulations *

Unfortunately the dividends from formal exercise are quite small and are not worth the discomfort or effort Newburgh has estimated that it requires a hike of 26 miles to burn one pound of body fat Sports and physical play are, however, useful and beneficial as a means of draining accumulated emotional tensions They may provide a hobby or interest which will dissipate boredom unrest, and other emotional conditions conducive to overeating

* See Chapter 45

assessed gently The *patient then is* instructed to perform postural exercises, such as, assumption of the knee chest position for ten to fifteen minutes two or three times daily Rarely will the uterus fail to come out of the pelvis by the end of the twelfth week of gestation If retention of urine and/or *signs and symptoms of threatened* abortion develop at about this time, and an incarcerated, retrodisplaced uterus is found, prompt reposition under anesthesia with insertion of a Smith or Hodge type pessary is required

During the examination of the adnexae any ovarian enlargement is searched for, although one must be careful not to confuse the corpus luteum with a pathologic cyst If one ovary appears suspiciously enlarged, the patient should be re examined in two or three weeks Solid tumors of the ovary are better removed during the second trimester

Pelvic Measurements

External measurements, while not accurate as to the pelvic inlet, do give the physician an idea of the general type of the pelvis and may detect the presence of an occasional asymmetrical pelvis As to the outlet, the physician should be able to insert his clenched fist between the lowermost extremities of the ischial tuberosities The *angulation of the pubic arch* should be close to 90° Internal examination first of all permits detection of the length of the diagonal conjugate If this is not easily done on the nulliparous patient at the time of the first visit, it must be repeated later in pregnancy Probably of greatest importance in the present day woman is the evaluation of the mid pelvis, including the lower sacrum The prominence and distance between the ischial spines should be approximated, and *their relationship to the sacrum* noted A prominent lower sacrum, present because of angulation at the midpoint, or because of general flattening, may mean midpelvic contraction The posterior bony pelvis above is best evaluated on rectal examination, which at the same time will help *in the pelvic examination* in general and will reveal the presence of any hemorrhoids or fissures which may cause trouble in later pregnancy

Roentgen ray pelvimetry has received increasing attention of late and may be of aid in an occasional case It should be emphasized, however, that the pelvis is but one factor in determining success or failure in any labor, and rarely the principal one Expert interpretation of radiographic findings *in relation to a particular cephalopelvic* relationship is an absolute prerequisite to success

Laboratory Work-Up

There is no value in delaying the collection of blood for blood count, perhaps hematocrit, blood serology, and Rh factor as well as blood group determination If Rh negative blood group is found, the husband s blood should be tested for the Rh factor *If there is a conflict in the Rh types* and the wife is negative, the wife's blood should be examined for antibodies early in the pregnancy, if this is the second gestation or a later one, or if there is a history of transfusion In this regard abortions may sensitize the patient Complete urinalysis on a voided specimen should be done on the first visit, and the patient must have a roentgen ray examination of the chest

RETURN VISITS

The patient must be instructed to see the physician once every three weeks until about the thirtieth week of amenorrhea and every ten to fourteen days thereafter If the pregnancy appears to be continuing beyond the calculated due date, the patient should be seen every week A specimen of the patient's first voided morning urine should be examined for albumin and reducing substance The weight should be

well as details of its management often depend to a large extent upon what might seem to be obscure details in the patient's early childhood history, or even in the history of her family background

The obstetric careers of the patient's mother and her sisters are important elements In the patient's own past history the inquirer searches for details of such illnesses as tonsillitis fever chorea rheumatic fever, cardiac or pulmonary disease and allergic disease If abdominal operations have been performed complete details of these operations from the patient are necessary Such information may even be obtained from the physician who performed the operation, or the hospital at which it was done Menstrual history includes specific details on the patient's last menstrual period as well as the preceding menstrual period The normalcy of these may determine the expected date of confinement the possibility of impending abortion or of the presence of an ectopic gestation

A complete obstetric history will reveal the circumstances of any miscarriages as well as pregnancies terminating in deliveries Included in such inquiries is a search for the details of each labor, as well as any complications that may have arisen at any time Thus one may learn of blood transfusions The patient's symptoms in the current pregnancy are of course, important, not only as they concern the pregnancy but other conditions One should ask specifically about nausea vomiting bladder disturbances constipation edema excessive weight gain cough dyspnea dizziness usual discomforts and especially, vaginal bleeding during the present pregnancy

Physical Examination

Though the patient may appear to be in perfectly good health a most thorough physical examination is essential with particular attention being paid to the general body type of the patient, her weight and blood pressure, the height, condition of the teeth and tonsils The thyroid gland should be examined for adenomas, though some diffuse enlargement is not unusual The heart is always very carefully examined and any murmurs noted for future re-examination If cardiac disease is present some tests for cardiac reserve are indicated When the breasts are examined the nipples deserve special attention The abdominal examination includes in particular a search for hernias, scars, and tumors The lower extremities in particular are inspected for varicose veins, especially in the popliteal areas over the calves and on the posterior thighs

Vaginal Examination

Complete pelvic examination with the patient properly draped in lithotomy position must be carried out meticulously There should be no postponement though the patient is at the time manifesting some symptoms of threatened abortion External examination should search for vulvar varicosities lacerations and old scars, Bartholin cysts or abscesses vaginal discharge, and excoriation The presence or absence of any cystocele, rectocele, or tendency toward prolapse should be determined Speculum examination for signs of vaginitis* and for condition of the cervix must be carried out in every instance Any lesion on the cervix, or polyp in the endocervix, which bleeds upon sponging with cotton on the end of sponge carrying forceps should be looked on with suspicion and a biopsy performed at once or in the very near future Bimanual palpation of the body of the uterus normally reveals its size consistency irregularity as to the presence or absence of fibroid tumors and position

If a retroversion of the uterus is discovered, the mobility of the organ may be

* See Lower Tract Infections Chapter 35

be discouraged at other times unless clearly indicated

Exercise

The patient should exercise in general as much as she has in the nonpregnant state No excess to the point of true fatigue should be allowed, nor should a patient who has led a sedentary life suddenly attempt to become very active Moderate amount of exercise is needed, and violent exercise in any form or strenuous athletic activity should be avoided Walking is the best form of exercise and should be encouraged

Bathing

Sponge and shower baths *may be taken* at any time during pregnancy Tub baths should be avoided during the last four weeks of gestation

Care of Breasts

Compression of the breasts in any form should be avoided, but an adequate breast *supporting* type of brassiere is indicated if the breasts are large The skin of the breasts should be washed daily with soap and water The anointing of the nipples daily during the last weeks of pregnancy with cocoa butter, cold cream, or lanolin, while unnecessary, will probably do no harm If the nipples are flat, they should be drawn out gently in late pregnancy If tenderness of the nipples is a prominent symptom, brisk but not too vigorous daily rubbing with a turkish towel *should be carried out*

Sexual Intercourse

Intercourse during pregnancy is generally restricted to an adequate degree by the tacit desire of both parties, such is advisable at any rate The patient should be advised that a deterioration of the *pleasure of intercourse* is a natural phenomenon and need not be permanent Coitus should be entirely eliminated during the last four weeks of pregnancy, and sooner if *any bleeding ensues*

Care of Teeth

The teeth should be examined and probably cleaned by a dentist at least twice during the pregnancy Any necessary dental work should be carried out Local anesthesia is not contraindicated The patient *should brush her teeth* after each meal, and particles of food between the teeth should be removed carefully with dental floss Gums may have a tendency to bleed massage with the fingers may be helpful, although dental care may be indicated

Coming to the Hospital

As the end of pregnancy approaches, the patient must be instructed as to when to go into the hospital Though individual circumstances differ, the patient should enter the hospital if brisk bleeding is noted or if the bag of water breaks Regular contractions every five minutes for the primipara, and every ten minutes for the multipara, should be the signal for going to the hospital

"Morning Sickness"

In the neighborhood of 40 per cent of women today have some nausea and/or vomiting in the first twelve weeks following conception Generally the distress is not severe but is still disturbing Mild measures usually overcome the difficulty Instead of eating the customary three meals a day *the patient should eat small amounts* of food every two hours The food should be solid and preferably carbohydrates Some pregnant women who have nausea dislike sweets and starches at this time They should eat whatever appeals to them or at least what is not repulsive to them Water should not be taken with the meals but about an hour after eating In some cases of morning vomiting, eating dry crackers or dry toast before getting out of bed helps

determined under similar circumstances at each visit and recorded Blood pressure determination likewise should be carried out carefully

At the time of the return visit the physician should allow the patient to ask any questions which she may have and he should question her regarding her health in general and specifically in regard to such things as swelling of the extremities or face persistent headache constipation, vaginal bleeding, symptoms of bladder irritation, excessive dyspnea, and persistent nervousness or insomnia

Excessive gain or loss in weight must be evaluated at each visit keeping in mind the patient s ideal weight as a baseline A total gain of 6 5–7 Kg above this ideal or normal figure is desirable The patient should be instructed to gain no more than half a pound per week after the third calendar month, until the last six or seven weeks of pregnancy when she may gain as much as three quarters of a pound per week Weight gain that is double or more than this suggested normal should focus the physician s attention to the possibility of water retention and impending toxemia

DIET

*The pregnant patient s average daily in*take during the last five months of pregnancy should be in the neighborhood of 2000–2400 calories with a daily protein intake of 80–85 Gm Sodium in the form of table salt, sodium bicarbonate etc should be curtailed in the last half of pregnancy A quart of milk in some form, and somewhat over a quart of water should be taken every day

The average diet is adequate in all minerals and vitamins with the possible exception of vitamins A and D These may be added in the form of capsules If milk is *taken as noted there is no need for supple*mentary calcium

Anemia of late pregnancy is primarily a result of blood dilution, but some true iron deficiency may exist Prophylactic administration of iron alone or in combinations in the last trimester has proved of value in many cases *

COMMON PRENATAL PROBLEMS

Care of Bowels

In avoiding constipation, the patient should be advised to drink plenty of water and to set a regular time to have a bowel movement A large amount of fresh fruits and vegetables, as tolerated should be eaten A glassful of prune juice in the morning is often of considerable assistance If these measures do not suffice, the patient should take an ounce of mineral oil milk of magnesium mixture at night or a tablespoon of "metamucil" Glycerin suppositories in advance may be of assistance as term approaches An oil retention enema should be the last resort

Urinary Frequency and Vulvar Irritation

In the presence of frequency of urination or vulvar irritation one should look for vaginitis particularly *Monilia* infestation Urinary frequency without signs of vaginitis or vulvitis, particularly when accompanied by fever and kidney or ureteral *tenderness indicates true urinary tract in*fection Treatment of both conditions is discussed elsewhere

Leukorrhea

A mucus like vaginal discharge may be expected off and on through pregnancy and is more noticeable as term approaches In the absence of symptoms, no particular treatment is indicated Symptomatic leukorrhea should suggest the presence of trichomoniasis or moniliasis and appropriate treatment as discussed elsewhere should be carried out † Douches are to be avoided in early and in late pregnancy, and should

* See Chapter 14
† See Chapter 9

If the bleeding continues after a week or ten days, or becomes more severe, in all likelihood the abortion is inevitable A careful pelvic examination will determine if the size of the uterus is consistent with the period of amenorrhea If it is not, one can assume that the pregnancy is no longer viable The *patient s activities should no* longer be restricted

Inevitable Abortion

Inevitable abortion is characterized by continued bleeding increasing severity of the cramps, the loss of amniotic fluid, the passage of large clots and some dilatation of the cervix In some women the initial symptom is a profuse hemorrhage In others who have had symptoms of threatened abortion it may take several weeks or longer to establish the fact that the abortion is inevitable

Treatment The patient who has profuse bleeding should have a curettage promptly, for this is the only way that bleeding can be brought under control Parenteral fluids should be administered promptly, while preparations for replacement of blood are proceeding It is rarely necessary to pack the uterine cavity, the removal of all the products of gestation *and the administration of posterior pitu*itary extract will stop the hemorrhage An oxytocic drug such as ergonovine maleate 0 2 mg *can be given orally twice daily for* several days The patient can be out of bed the day after the curettage and fully ambulatory at the end of four or five days

When symptoms of slight bleeding and cramps have persisted for days or some weeks curettage should be postponed until it is certain the pregnancy is no longer viable, the uterus should have decreased to less than the size of an eight weeks' gestation, and there should be some cervical dilatation Premature attempts at the evacuation of the uterus in the absence of a critical indication may result in much blood loss and an increased hazard to the patient

Incomplete Abortion

Incomplete abortion is present when some portions of the gestation still remain in the uterine cavity Often it is a hemorrhagic, degenerated chorionic sac, at other times fragments of the placenta If there is no evidence of infection then it is safe to do a curettage However, in the patient who has a fever, foul discharge, or a history of previous manipulation, surgical interference should be postponed until the infection is quiescent unless hemorrhage necessitates active treatment

Infected Abortion

Infected abortion is the most common sequel of attempts to terminate an unwanted pregnancy In some women trauma as well as infection complicates the problem The patient who has a history of a criminal abortion or who has fever or evidences of peritoneal irritation should be treated guardedly

Careful examination should be made to determine the size of the uterus, the extent of the infection, and evidences of trauma A bacterial culture of the uterine contents will help in the selection of the proper antibiotic At this examination it is permissible to remove clots and fragments of tissue occluding a patulous cervical canal No exploration of the uterine cavity or curettage is advisable at this time unless *the blood loss is threatening*

Treatment Antibiotic therapy should be instituted In that several pathogenic *organisms are usually involved in these in*fections more than one antibiotic may be indicated Anemia should be combatted *by blood transfusion Peritoneal* irritation or frank peritonitis calls for the typical regimen of gastrointestinal drainage, nothing by *mouth*, and ample parenteral fluids 'Pitocin," 10 units administered in

A mild sedative such as mixed bromides (1 Gm three times a day) or phenobarbital (30-mg tablet three times a day) often aids considerably Rest and quiet are sometimes helpful, but it is important for the patient to occupy her mind with matters other than the pregnancy

During the past three or four years one of the so called 'seasickness remedies has received extensive trial in this condition In doses of 50 mg three or four times daily it appears to help some patients Amphetamine compounds may be used simultaneously to counteract sedative effects

Rarely if the patient cannot retain even clear liquids hospitalization is necessary Hyperemesis is usually cured quickly if treatment by hydration definite sedation with isolation, and adequate parenteral carbohydrate is instituted promptly Vitamins must not be neglected

Psychologic Preparation of the Patient

In the present day practice of maintaining a natural attitude toward pregnancy and labor the patient must be properly prepared mentally and psychologically Without the elaborate group education setups of large institutions doctors in their own offices can do much

Education concerning pregnancy and labor delivery as a *physiologic* process is the first step

Simultaneously must come the dispelling of fear and tension particularly in regards to labor Pain relief should be discussed and confidence instilled into the patient—that the physician will be on hand that her needs will be attended to The patient must be warned against accepting advice from anyone except the physician

HEMORRHAGE IN EARLY PREGNANCY

Once a patient conceives she should have no bleeding during her entire pregnancy Menstruation does not occur following conception Bleeding is always the result of some pathologic process During the *first trimester it is usually the result of* abortion or, more rarely, ectopic gestation Hydatidiform mole and chorionepithelioma are very rare complications A cervical polyp an erosion or the rupture of a small varicosity must be ruled out by examination

Intelligent management of this complication entails a correct diagnosis The history of one or more missed menstrual periods is significant in the diagnosis of pregnancy An enlarged softened uterus on pelvic examination is usually indicative of gestation The visualization of the vagina and cervix by means of a speculum will rule out local conditions which may be the cause of the bleeding A carefully conducted pelvic examination will not increase the hazard of abortion and will provide valuable information for intelligent therapy

ABORTION

Abortion most often occurs in the first three months of pregnancy but it may not take place until midgestation

Threatened Abortion

Threatened abortion is characterized by bleeding and, occasionally, by uterine cramps In most women who exhibit these symptoms the gestation is no longer viable and may have succumbed days or weeks previously In no more than one out of four women with threatened abortion will the pregnancy continue It is for this reason that definitive therapy will not alter the course of events

Treatment The patient who begins to spot or bleed in early pregnancy should be put to bed for a few days Coitus and drastic cathartics should be avoided Mild sedation may be prescribed Endocrine therapy is not indicated

tions the pregnancy is in a fallopian tube The diagnosis of this condition is the salient feature in successful therapy

The most pertinent information in the patient s history is the missed menstrual period followed by vaginal bleeding and discomfort or severe lower abdominal pain Pelvic examination will reveal the local findings of early gestation as well as a tender adnexal enlargement lateral to the uterus Sometimes there is sufficient utero abdominal bleeding to cause bulging of the cul de sac Tubal rupture is characterized by acute abdominal discomfort as well as symptoms and signs of hemorrhage into the peritoneal cavity Aspiration of the cul de sac by means of a large needle on a syringe will reveal free blood in the pelvic cavity

Blood replacement prior to during and after the surgery is a most important part of the management of ectopic gestation The operation should not be postponed in the patient in shock until blood is available for it is necessary to stop the bleeding promptly However every effort should be made to obtain blood while parenteral fluids are being administered The surgery should be limited to the remov
abnormal pregnancy in most pati

The postoperative care is usually
plicated If there is any likelihood o
tion prophylactic antibiotic therapy
be instituted The patient is encoura
be up and out of bed for a few minu
day following surgery Therapy for a
may be necessary

THERAPEUTIC ABORTION

Therapeutic abortion has become
creasingly less common with continued
vances in medicine The law and medic
ethics permit the termination of pre
nancy when its continuation would jeop
ardize seriously the health and life of the
patient Cardiac disease and vascular renal
disease are the most common indications
although rarely other complications may justify the procedure Termination of the pregnancy is most often done abdominally by hysterotomy so that some procedure to prevent future child bearing can be carried out at the same time For members of the Catholic faith it may be necessary for the physician to explain the necessity for interruption of pregnancy to the patient s spiritual advisor

Toxemia of Pregnancy

THE term toxemia of pregnancy is one
which includes not only pre eclampsia and
eclampsia but chronic hypertensive vascular
isease with a superimposed pregnancy
he former two conditions which consti
te about 40 to 50 per cent of all toxemias
peculiar to pregnancy almost always
pear during the latter half of the period
estation and are characterized by hyper
ion proteinuria and edema Actually
eclampsia and eclampsia are but differ
manifestations of the same condition

The importance of the early recognition and institution of treatment is emphasized by the mortality rates which increase from 0 4 per cent for the mild cases to an average of 13 per cent for eclampsia

In the well-developed case it is impossible to distinguish pre eclampsia from chronic hypertensive vascular disease On the other hand there are points of difference which may be discovered after the pregnancy or early in the course of the disease The typical patient who has pre

tramuscularly, or ergonovine maleate, 0 2 mg orally, may aid in the expulsion of the uterine contents and will help to maintain uterine tone

Curettage may be done after all evidence of infection has subsided for at least four or five days It may become necessary at any time because of profuse bleeding Suppura tion may be a late complication An abscess may develop in a parametrium or in the cul-de sac and drainage will become neces sary

In some patients who have septic abor tions thrombophlebitis is a serious compli cation The clinical course is characterized by chills fever, a rapid pulse, and occasion ally embolic infarction of the lungs Pelvic examination may be entirely negative though one may occasionally palpate thrombosed vessels in the parametrial areas Collins has suggested ligation of the ovarian vessels and vena cava if the patient does not improve in three to five days of ade quate antibiotic therapy or if lung infarc tion develops

Complete Abortion

Complete abortion has occurred when all of the products of gestation have been passed Usually bleeding is diminished and the uterus contracts firmly In many insti tutions a curettage is performed if the pa tient is seen within twenty four hours following the abortion and has no infec tion This is done to insure that the uterine cavity is clean thus favoring a rapid and uneventful *recovery*

If no curettage is done the activity of the patient should be restricted for four or five days She can be given ergonovine maleate 0 2 mg orally two or three times a day for several days If there is an anemia, appropriate medication should be insti tuted Coitus and douches must be avoided for at least two weeks after all bleeding has subsided

Habitual Abortion

Habitual abortion is defined as the third or more spontaneous consecutive abortion in an individual The likelihood of such a patient continuing a pregnancy to a suc cessful conclusion is no more than 16 or 18 per cent In most women no obvious cause for these repeated abortions is evident, al though there may be a recurrent factor in each pregnancy

Treatment. Treatment has been empir ical and is usually directed toward provid ing additional hormonal support for the pregnancy A complete physical examina tion including a basal metabolism of hus band and wife should precede pregnancy All physical abnormalities that can be cor rected should be eliminated The patient should be encouraged to eat a high protein diet for several months preceding the preg nancy and to continue this after conception

During pregnancy coitus douches, or drastic catharsis should be avoided Physical activity should be restricted but normal living habits can be continued Liberal amounts of thyroid extract to toler ance can be administered if the basal rate is below the normal level Progesterone in oil, 50–100 mg may be administered intra muscularly every day from the time the diagnosis of pregnancy has been established until at least two weeks after the third missed menstrual period If previous abor tions have occurred at mid pregnancy, the progesterone should be continued for a longer time Oral therapy with progesterone has not been successful

Graduated amounts of diethylstilbestrol beginning at 5 mg daily and increasing to 125 mg at the end of the gestation have been recommended This medication has not proved as successful as progesterone in our experience

ECTOPIC PREGNANCY

The definitive treatment of ectopic preg nancy is its termination With few excep-

TABLE 50 SIGNS AND SYMPTOMS OF TOXEMIA

GROUP A (SIGNS)
Edema (weight gain), Hypertension, Proteinuria

GROUP B (SYMPTOMS)

Cerebral	*Visual*	*Gastrointestinal*	*Rena*
Headache	Diplopia	Nausea	Oliguria
Dizziness	Scotomata	Vomiting	Anuria
Tinnitus	Blurred vision	Epigastric pain	Hematuria
Drowsiness	Amaurosis	Hematemesis	Hemoglobinu
Amnesia		Jaundice	
Change in respiratory note			
Tachycardia			
Fever			

GROUP C (CONVULSIONS, COMA)

clinical findings of toxemia (Group A) but no symptoms, hospitalization is unnecessary but a carefully outlined regimen of therapy and frequent observation is of utmost importance Treatment is directed toward reversing or at least stabilizing the findings preventing the occurrence of eclampsia If careful medical management is begun at an early stage in the disease, increase in severity can in most cases be prevented, at least until induction of labor is feasible

The effectiveness of the office treatment of the mild pre-eclamptic may be gauged by (1) control of weight (edema), (2) control of blood pressure, (3) maintenance of urine output, (4) stabilization of the twenty four–hour protein excretion, and (5) prevention of symptoms

Since fluid accumulation in the tissue spaces is a direct result of abnormal retention of salt, a reversal may be anticipated if the sodium chloride content can be reduced, thus freeing the water This may be ccomplished by a "pre eclamptic diet' hich contains less than 2 Gm sodium loride daily If the patient adheres strictly this diet the tissue electrolytes will be lized by the body and the excess water ch was holding them in solution will excreted, thus both relieving the edema supplying fluid to the kidney for the formation of urine Ammonium chlori in dosages of 8 Gm daily may increase t rapidity with which the fluid is release Mild sedation with phenobarbital (6 mg three times a day and at bedtime), menta relaxation, and at least ten hours in bed daily will aid in preventing further elevation of the blood pressure Blood pressure determinations and weights should be taken at weekly intervals and the measurement of the twenty four–hour protein excretion should be made at least twice weekly Success in control on this regimen is indicated by a regression or failure of progression of the signs of toxemia Failure is indicated by

1 Progressive increase in blood pressure,
2 Progressive gain in weight or an increase in the amount of edema,
3 Increase of proteinuria,
4 Development of symptoms (Group B)

Such a failure makes hospitalization and the institution of more active therapy imperative

Hospital Management

Advance in severity of the toxemia is characterized by a progressive diminution in urinary output with an increase in total protein, further elevation of blood pressure, hemoconcentration as indicated by an in

eclampsia eclampsia is a primipara under 25 years of age whose blood pressure before pregnancy and between subsequent pregnancies is normal She will have gained greater than 25 pounds of weight during the pregnancy show marked edema and be free of definite symptoms until the last trimester—usually until the last four to six weeks of gestation The typical patient with essential hypertension will be a multipara of the average age of 33 years, with a blood pressure greater than 140/90 before pregnancy She may or may not have some edema at the height of the disease, will have gained less than 20 pounds and will have manifested symptoms in the first half of pregnancy or in the middle trimester

The pre-eclamptic will probably not have a family history of hypertension will not respond well to bed rest since the blood pressure is not labile and will have a lower blood pressure at the height of the syndrome—especially with convulsions The hypertensive will be the opposite in each of these criteria Dieckmann does not believe that pre eclampsia may be superimposed upon hypertension as do many workers in the field but feels rather that pregnancy causes an increase in the severity of the chronic hypertensive vascular disease

Although our knowledge of these conditions has been increased tremendously by the volume of investigation carried out over the years the etiology is as yet undetermined and pre-eclampsia cannot be prevented however its course can be modified by early diagnosis and judicious care thus forestalling its progression to the convulsive state

Almost all cases present minimal early signs, the first of which is an abnormal gain in weight We believe that the optimum total weight gain for normal pregnancy is 6 5–7 Kg and that gains of more than 0 2 Kg weekly during the last half of pregnancy indicate an abnormal retention of water In almost all instances a period of abnormal weight gain precedes the appearance of edema Although slight ankle edema is not uncommon in normal pregnant patients pitting edema over the tibiae is an indication that fluid retention is greater than the expected amount

Elevation in blood pressure above 140/90 or a total increase in systolic pressure of 30 mm Hg is indicative of abnormality The blood pressure is not necessarily increased to alarming levels in pre eclampsia or even in eclampsia, the mean systolic pressure in the former group being 147–169 and the latter 174 Hence a feeling of complacency concerning any patient with signs suggesting pre eclampsia even though the blood pressure is only slightly elevated is unwarranted

The total amount of protein excreted in a twenty four-hour urine specimen by the normally pregnant patient is less than 0 6 Gm This is increased in pre eclampsia and the more severe the condition the greater the amount of protein put out by the kidney The common method of estimating the amount of proteinuria by grading the reaction from + to +++ may at times be misleading for instance a given amount of protein in 2000 cc of urine may be read as + whereas the same amount in 500 cc may be +++ consequently, the quantitative measurement of the total twenty four-hour excretion is a more accurate indication of the renal function and should be carried out in all patients with toxemia

TREATMENT OF PRE ECLAMPSIA

Ambulatory Management

The signs and symptoms of pre eclampsia have been divided into groups which indicate progressive severity of the condition and which may be utilized as an aid in guiding treatment (Table 50)

In the usual patient who has only the

should be considered only in the patient in whom there is a contraindication to delivery from below (cephalopelvic disproportion) or in the face of severe eclampsia in a patient with a long closed cervix. Initial treatment by delivery by any means without a preliminary period of medical control of the disease is associated with an alarming maternal mortality; hence control of convulsions and reestablishment of renal function must precede delivery.

SUMMARY

The recognition of the earliest signs of pre-eclampsia and the prompt institution of adequate treatment will in most cases prevent the progression to severe pre-eclampsia and eclampsia with decrease in maternal and fetal The treatment of pre-eclampsia toward maintenance of normal r tion and reversal of the abnor exchange between blood stream an

The most important factors in trol of eclampsia are the use of hy glucose solutions to reestablish renal function and to relieve e edema, and sedation to control convu While delivery is important, the su rate can be increased by obstetrical agement, that is a period of medical trol followed by termination of pregnancy at a time when it is least dan ous for the mother.

Treatment of Chronic Hypertensive Vascular Disease

THE hazards of chronic hypertensive vascular disease are fetal death, abruptio placentae, impairment of renal function, cardiovascular accidents and eclampsia, but approximately 60 per cent of women will go through pregnancy successfully. In the remainder a progressive deterioration of their vascular-renal system takes place, manifested chiefly by an elevation in the blood pressure and increasing amounts of albumin in the urine. The superimposed pregnancy is directly responsible for this development, so that many clinicians feel that this represents pre-eclampsia superimposed on an abnormal vascular-renal mechanism.

The interruption of pregnancy and some surgical procedure for the prevention of uture gestations is indicated in a few pa ients who are seen sufficiently early and ho exhibit one of the following complica ons:

Marked impairment of renal function
Marked hypertension associated with cardiac enlargement or evidences of cardiac failure
3. Old retinal exudates and evidences of fresh retinal hemorrhages
4. Progressive rise in blood pressure associated with increasing proteinuria. A continued daily output of more than 5 Gm of albumin in the urine bodes ill for the survival of the fetus.

All patients with chronic hypertensive vascular disease should be admitted to the hospital for a careful and meticulous study of heart size, retinal changes, kidney function and the pattern of hypertension under rest and sedation. If it is decided to allow the pregnancy to continue, a medical regime comparable to that used in the management of hypertensive disease should be instituted.* The nutritional requirements of the growing fetus and its developing environment must be kept in mind. Thus an adequate intake of proteins, minerals and vitamins must be assured. Weight gain

* See Chapter 15

crease in cell volume and red cell counts, and in many cases the appearance of symptoms which become progressively more pronounced Severe pre eclampsia is characterized by (1) two or more of the following repeated blood pressures greater than 160/100 mm Hg, proteinuria more than 0 3 Gm per 100 cc, or marked edema, (2) at least one of the following repeated systolic blood pressures greater than 185 mm Hg, proteinuria more than 0 5 Gm per 100 cc, or generalized edema, or (3) one of the signs in (1) accompanied by cerebral, gastrointestinal, visual, or renal symptoms

The initial hospital treatment of pre eclampsia concerns itself primarily with the classification of the severity of the condition and the initiation of a regimen designed to control the signs and symptoms With the exception of an evaluation of the duration of pregnancy, the size and position of the fetus, and the adequacy of the pelvis, the pregnancy is, at the onset, ignored

Medical Care

The most important factor in the management of severe pre eclampsia is the maintenance or promotion of urine output which is diminished as the fluid components of the blood are drawn from the blood vessels into the tissues This is an essential step in the prevention of eclampsia and in most instances can be achieved by the proper use of hypertonic glucose solutions which reverse the fluid exchange, drawing the edema fluid back into the blood stream The concentrated blood is thus diluted, making available fluid for the kidney to excrete The decrease in tissue fluids aids in diminishing the cerebral symptoms and in preventing convulsions Since the purpose of the glucose is to increase osmotic pressure in the vessels and thus draw fluid from the tissues the solutions must be administered rapidly (within forty to sixty minutes) in order to produce as high a blood level as is possible Approximately 200 Gm of glucose produce the best diuretic response, this usually is administered as a 20 per cent solution of which 1000 cc is given Great care must be taken to prevent tissue infiltration The injection may be repeated two or three times daily to maintain an adequate output

The mercurial and xanthine diuretics are of no value in correcting the oliguria because their action is directly on the kidney, unless the hemoconcentration is corrected by reversal of the fluid exchange, no increase in urine can be anticipated Careful records of fluid intake and urine output are essential as an aid in determining the effect of therapy

Daily quantitative determination of the total protein excretion likewise is of prognostic significance A steady increase or a constant excretion of more than 3–5 Gm daily is a grave sign indicating a failure of medical treatment to control the disease Daily protein excretion greater than 5 Gm is associated with a definite increase in intrauterine fetal death

Bed rest and sedation with phenobarbital will aid in controlling the blood pressure, which should be recorded twice daily

Obstetric Management

If the response to this regimen is favorable, that is, if an adequate urine output (1200–1500 cc) is maintained, the proteinuria does not increase, the blood pressure is controlled, and symptoms improve, the patient may be carried until the cervix is 'ripe, at which time labor should be induced by rupture of the membranes and the injection of 0 06 cc doses of 'pitocin" at thirty minute intervals if contractions have not begun in twelve hours 'Pitocin" is used rather than pituitrin because of the relative absence of the antidiuretic principle in the former preparation

The decision as to when the cervix is ripe is of utmost importance, since rupture of membranes before conditions are

branes without uterine contractions and for the amelioration of discomfort and tension of premonitory or early labor, the patient may be given up to 0 2 Gm of one of the shorter acting barbiturates seconal or amytal sodium or pentobarbital When progressive labor has begun in earnest and the patient shows signs of distress definitive analgesia amnesia must be instituted In a primipara this point should be not before 3–4 cm of cervical dilatation has been attained and contractions of 40 to 50 seconds duration are occurring at three to five minute intervals In multiparas dilatation is of lesser importance but contractions must be strong and regular

Many technics and drugs have been recommended for pain relief during first stage * The authors prefer to give subcutaneously 10 mg morphine sulfate and 0 5 mg scopolamine Repetition of the morphine is not recommended unless labor is of unusual duration Scopolamine may be repeated at intervals of forty five to ninety minutes in dosage of 0 3 mg as is necessary to maintain the parturient in a drowsy state of semiconsciousness This technic is usually satisfactory for maintenance of amnesia through the first stage of labor Morphine should not be given if delivery is anticipated in less than three hours

An alternative technic involves the use of demerol in place of morphine under the criteria outlined above Initial dose should be 100 mg of demerol with 0 5 mg scopolamine Demerol in the same amount may be repeated in one to two hours with 0 3 mg scopolamine if amnesia is not complete No more than 0 3 Gm of demerol should be given in any one day Methadone (10 mg) is likewise an adequate substitute for morphine

At or near completion of cervical dilatation the patient may be given inhalation or regional analgesia Open drop ethyl ether with a gauze covered wire mask is the most convenient agent and probably the safest On the other hand it is not so efficient or pleasant in creating analgesia intermittently with recurring contractions We prefer ethylene or nitrous oxide with oxygen for this purpose

When delivery is imminent the anesthesia is deepened in accordance with the type of procedure contemplated Deep surgical anesthesia is not necessary for spontaneous delivery or uncomplicated outlet forceps and/or episiotomy On the other hand complete muscular relaxation is required for version midforceps procedures and breech delivery by extraction

Experience in over 5000 cases has shown that the average physician may use with safety saddle block spinal anesthesia during the second stage and for delivery This simple and precise technic creates sensory relaxation of perineal and pelvic muscles as well as the cervix and lower uterine segment Painless uterine contractions continue unslackened but the patient s urge to bear down is lost Low or outlet forceps deliveries are the rule under this technic Drugs principally used are nupercaine (2 5 mg) and metycaine (30 mg)

Any physician who practices obstetrics should master and utilize the technique of local infiltration and pudendal block anesthesia This safest of all anesthetics is suitable for episiotomy and low forceps procedures as well as spontaneous delivery The use of hyaluronidase to augment the local anesthetic agent (generally 1 per cent procaine hydrochloride) will make for greater technical success and more complete relief of discomfort in pudendal block

The physician must be prepared to modify his usual methods of analgesia and/or anesthesia when faced with complications of pregnancy and labor which affect either or both the maternal and fetal organisms In some instances the use—or avoidance—of a particular drug or technic becomes

* *See also Chapter 27*

and salt intake should be restricted as much as possible Rest periods during the day are advantageous Phenobarbital in moderate amounts will decrease the effect of everyday stimuli and allow for more real relaxation and sound sleep

An exacerbation of the findings of toxemia such as an elevation of the blood pressure or increasing proteinuria or the development of symptoms listed in group B Table 50 calls for the hospitalization of the patient

If the signs of chronic hypertensive vascular disease remain quiescent one can await the natural onset of labor However in many of these women the progress of the disease makes early termination of the pregnancy highly desirable The earliest period in the gestation when fetal survival is likely is about eight weeks from term Although each additional week increases the likelihood of fetal survival the continuation of the pregnancy may increase the hazard to the mother s life Furthermore, intrauterine death of the fetus is a frequent occurrence

Most women are multigravidas and conditions may be favorable for the induction of labor by the rupture of the membranes If the findings on pelvic examination do not warrant the induction of labor, or if the induction of labor fails, cesarean section and tubal ligation may be the procedure of choice

Anesthesia and Analgesia in Labor

THE average American woman will to a variable degree experience pain during the process of labor The variability depends to a great extent on the woman s inborn tolerance to pain and the degree of fear and tension that she takes with her through pregnancy and delivery The physician may modify the latter factors by proper prenatal education toward consideration of pregnancy and delivery as physiologic and not pathologic processes Increasing the patient s confidence in herself and in her physician will serve to diminish the intensity of labor pains

Completely painless childbirth of any particular type should not be promised any woman but relief compatible to the well being of the patient and that of her baby should be maintained Anesthesia for delivery is a precise procedure and the type depends entirely upon the presence of one qualified to administer the anesthetic of choice, while, for analgesia amnesia, there are several technics which will give satisfactory relief to 85 to 95 per cent of all women Regardless of the agents or technics used each physician should establish for himself a rational plan of procedure This should not be a routine method applicable in identical fashion to all patients and to all labors, nor should it be expected that such a plan would be an extremely simple one suitable for the use of physicians who see their patients in the hospital during labor only in time to accomplish terminal delivery

This rational plan for management of each patient s needs for psychologic support and relief of pain includes proper prenatal education creation of confidence on the part of the patient close attendance to the labor as the parturient s individual personality and the character of her labor demand and finally, proper preliminary medication and definitive analgesia and anesthesia

During the period of anxiety or sleepless inactivity imposed by rupture of the mem

marginal sinus rupture etc and from mechanical pressure on the cord concomitant with prolapse and/or entanglement the physician should be prepared to deviate *from any formalized* routine for pain relief Narcotics should be limited, and anesthesia at delivery should be accompanied by oxygen administered at the greatest possible volume and rate This implies use of the pudendal block or other local infiltra*tion technics most of the time* Where there has been considerable hemorrhage before delivery or when hemorrhage is threatening to produce shock spinal anesthesia is best not used by the average physician On the other hand saddle block spinal anesthesia supplemented by prophylactic vasomotor pressor drug administration and accompanied by oxygen inhalation throughout the period preceding and during actual delivery, is definitely indicated in cases of prematurity This method may also prove of value for operative delivery in the face of cord complications Severe maternal anemia is another indication for the limitation of narcotic drugs and general anesthesia

Postpartum Care

POSTPARTUM care long has been a neglected phase of obstetric practice In recent years the advent of early ambulation and a tendency to consider the delivered mother a healthy woman convalescing from a normal function—reproduction—rather than a sick individual who will need prolonged bedside nursing has done much to improve the medical and nursing conduct of the puerperium There does remain however considerable room for improvement in the psychologic management of the delivered patient Every postpartum patient regardless of her parity requires guidance and information concerning the psychology of the period through which she is going She must learn to care for herself adequately and not to be concerned over normal variations She must be aided in the acceptance of a child or of another child so that she can fit the infant into the family unit and develop a wholesome mother child relationship that will be mutually satisfying At the same time there must be guidance away from equally as *vexing problems concerning* her psychologic relationship with her husband

IMMEDIATE CARE

Postpartum care begins with the instant of placental delivery and repair of any episiotomy The tendency for physicians to go about their business immediately after delivery and to neglect the recently delivered woman has brought about the development of postdelivery recovery rooms in some institutions Regardless of whether or not the care of the patient during the *first twenty four hours following delivery is* so formalized, watchful attention is in order Particularly important is the first post*partum hour It is during this period that* most fatal cases of postpartum hemorrhage first get out of hand The fundus of the uterus must be watched carefully by an experienced individual and palpated gently but frequently to note any tendency toward *persistent relaxation* Repeated doses of oxytocic drugs and massage associated with repeated episodes of considerable blood loss are inexcusable If one or two doses of ergonovine maleate 0 2 mg intravenously or intramuscularly following delivery of the placenta do not permanently control relaxation of the uterus *the patient must* be returned to the delivery table and the

mandatory while in others the variation is simply desirable

In active or recently active tuberculosis, asthma or acute respiratory infections, the avoidance of inhalation anesthesia in favor of local or terminal spinal anesthesia is necessary The care with which one follows the pregnant patient suffering from cardiac disease must be continued into delivery, and serious consideration must be given to the problem of anesthesia and analgesia Since tachycardia has been recognized as perhaps the earliest sign of impending trouble for the cardiac patient during labor, the use of scopolamine, which tends to produce tachycardia, is confusing and dangerous Morphine and barbiturates may be used during the first stage Delivery by low or outlet forceps is the method of choice and this procedure can be carried out under pudendal block anesthesia or local infiltration Only if the cardiac disease is in a mild degree of activity should inhalation anesthesia with ethylene or ether be considered entirely proper In this regard it should be repeated that cyclopropane has a tendency to produce ventricular arrhythmias

Saddle block spinal anesthesia should be the method of choice for those physicians who are thoroughly adept at this technic except where the patient is a severe hypertensive This form of spinal anesthesia which can be controlled to a level at about the umbilicus is helpful to the parturient with frank cardiac failure Bloodless phlebotomy by pooling of blood in the lower extremities and applying venous tourniquets can be carried out at will and the large amount of blood can be returned to the systemic circulation following delivery as slowly as is desirable by progressively releasing one or both tourniquets at any degree of speed while the legs are elevated

When the patient is a diabetic of any degree of severity general anesthesia might best be avoided particularly if it is to be used for operative delivery over a prolonged period of time Ether and thiopental sodium in particular are the least desirable of the systemic agents During labor agents which tend to increase any existing state of acidosis or which depress respiration should be limited

A patient suffering from any of the toxemias of pregnancy will probably require more barbiturates than usual during the first stage particularly 'amytal sodium' in 0 2 Gm doses Ether and ethylene should be avoided if the patient is in poor condition from the metabolic standpoint If the basis for the toxemia is essential hypertension rather than true pre eclampsia high spinal anesthesia is potentially dangerous A precipitous fall in blood pressure under these conditions may induce a fatal vasomotor collapse Local anesthesia should be used whenever possible and saddle block spinal anesthesia in pre eclampsia

The fetus that is unusually susceptible to hypoxia (principally the premature infant) and those subjected to acute or chronic oxygen deficiency during or before labor from one or several serious obstetrical complications, should be protected during labor and at delivery from respiratory depression This implies limitation of any narcotic drug for systemic analgesia and avoidance of inhalation anesthesia terminally

Above all the physician should avoid the potentially feticidal blow of narcotics and barbiturates plus general anesthesia in delivering small premature infants On the other hand the respiratory center of even a sturdy term infant may be so inhibited by nonfatal anoxic anoxemia from certain complications during labor that otherwise relatively minor degrees of depression from anesthesia may be the deciding factor in the production of severe asphyxia at birth When faced with danger to the fetus from hemorrhage of placenta previa abruptio,

neum with cotton balls and warm water As healing progresses and after removable sutures are taken out on the fifth day the cotton balls may be replaced with a wash cloth and soap suds The patient should be instructed always to cleanse the vulva and perineum from before backward to avoid contamination from the anus The practice of douching or rinsing the perineum with special solutions from a pitcher has been discarded A commercial sanitary pad held in place with a narrow belt is preferable to the old fashion T binder

The sutures are best kept dry Proper application of a heat lamp to the perineum will serve to promote healing and to alleviate discomfort of the repair Care should be taken however to avoid placing a lamp stand in such a position as to cause pressure on the popliteal spaces and thus promote injury to veins

BREAST CARE

It has become common practice to give no special treatment to the breasts following a soap and water cleansing at the time of the morning bath Nipples do better when they are allowed to dry out between nursing periods Should a crack develop the infant is not permitted to nurse for twelve to twenty four hours and the breast is exposed to a heat lamp and to open air as much of the time as possible Most nipple difficulties can be prevented if the baby is allowed to nurse for no more than five minutes the second postpartum day and is kept on a slowly progressive time schedule thereafter

If nursing is not to be carried out a tight binder is applied to the breast as soon as any engorgement is noted The binder must be applied in such a way as to hold the breasts upward and toward the mid line The administration of 5 mg diethylstilbestrol daily for seven days may serve to prevent some of the painful engorgement but there is reason to believe that the use of this drug may increase slightly the in dence of late postpartum hemorrhage a of delayed involution of the uterus packs may be applied to the breasts to h relieve the discomfort of engorgement drying out measures are practiced

GENERAL CARE

During the first two or three days pc partum the chest is examined for ea signs of atelectasis or pneumonia The domen is palpated twice daily for tend ness of the fundus and over the adne areas The legs are checked daily for ph bothrombosis or thrombophlebitis T development of any fever in the first fi postpartum days should be considered indicating endometritis until proven othe wise In addition to the measures of exam nation noted above the nose and thro must be checked for signs of upper respi tory infection the costovertebral angl pressed for signs of kidney tenderness ar the breasts examined for any atypical early mastitis A catheterized urine spec men should be obtained white blood cel in the urine are of little significance in th immediate postpartum period A signi cant number of bacteria must be presen in association with some kidney tenderne before the diagnosis of urinary tract infe tion can be made A tender uterus with c without bogginess in the presence of feve and in the absence of localizing signs els where in the body invariably serves t authenticate the diagnosis of endometriti Tenderness lateral to the uterus on eithe side usually indicates that the process ha spread from the uterus and has become parametritis

This form of acute postpartum pelvi inflammatory disease demands immediat and definitive treatment Most cases will re spond to penicillin therapy Dosage shoulc be at least 600 000 units twice daily unti the temperature has been normal for forty eight hours The patient should not be dis

entire birth canal explored for the cause of the bleeding During the first one or more postpartum hours the pulse of the patient must be taken frequently, and no woman whose pulse is over 100 should be taken to her room or away from the labor and delivery room suites Blood pressure readings likewise, must be taken during the first postpartum hour, since incipient shock *may thus be noted for the first time or a* hypertension may be discovered as the first sign of a postpartum toxemia of pregnancy

EARLY AMBULATION

When the patient has been returned to her bed, she is encouraged to move about freely and is given adequate pain relieving medication in order that free movement may be carried out readily Fluids by mouth are encouraged liberally unless the patient is extremely nauseated or vomiting from a general anesthetic The patient is given a soft or a general diet at the time of her first postpartum meal the type depending upon how many hours have elapsed since delivery During this early period, the nurse must watch the bladder quite carefully If the patient has the urge to void or seems to have the beginning of bladder distention within the first twelve hours following delivery it is perhaps best that she be given a bed pan If she is unable to void thereupon, however she may be helped to an adjoining bathroom or portable commode After the first twelve postpartum hours, the patient should be quite freely ambulatory Activity of the first two or three days should be restricted to the vicinity of her own room unless bathroom facilities require otherwise Frequent trips out of the bed for short periods of time should be the rule rather than few episodes of leaving the bed for prolonged periods Walking about the room is better than sitting Depending upon the available facilities and the general strength and well being of the patient a shower bath is best postponed until the third or fourth postpartum day Walking about the halls and visiting with other patients is usually allowed after the fifth day It is profitable to keep patients in the hospital for as long as ten days after delivery This allows the patient to regain a large share of her physical strength and to obtain confidence in her ability to return *home to the tasks that will face her*

BLADDER AND BOWEL CARE

If the patient seems to be voiding frequently in small amounts during the first postpartum day, she is catheterized for residual urine If the patient is unable to void over two successive eight hour periods it is advantageous to insert an inlying Foley bag catheter at the time of the third catheterization, leaving it in place for at least forty eight hours Following removal of the catheter the patient's voided amounts are watched carefully At least one residual urine below 75 cc should be obtained before the patient can be considered over her bladder difficulties It has been found that adequate sedation and pain relief will definitely diminish the number of bladder problems developing in the first postpartum day If the patient has had an enema at the time of admission to the hospital in labor, the postpartum period is generally free of bowel difficulties A laxative at night such as one ounce of mineral oil or milk of magnesia, beginning with the first or second postpartum night generally will obviate the necessity for an enema on the fourth day If the patient, however, has not moved her bowels adequately by this date, a saline or soap suds enema should be administered Liberal use of prune juice, with a supply kept at the bedside has served to further diminish bowel problems

PERINEAL CARE

From the time of the first voiding the patient is instructed in cleansing her per

35. Infertility and Gynecologic Treatment

M. EDWARD DAVIS
& GEORGE J. ANDROS

Infertility

FERTILITY in men and women varies widely depending primarily upon the age of the individuals their general health and the normalcy of their reproductive organs and the supporting endocrine glands Some of the less tangible factors involved are environment and emotions Failure of a woman to conceive at the end of a year of normal marital life justifies the physician in carrying out a complete sterility study *Although this period of infertility may be* considered short according to previous ideas the present attitude *is to ascertain the fact that* pregnancy is possible in all women who complain of inability to have children

A careful and complete diagnostic study of the sterile couple is the principal therapeutic tool in the treatment of sterility In the absence of major barriers to conception at least 30 to 35 per *cent of women become pregnant* within a year after a complete sterility investigation Thus in the *absence of definitive therapy for many of* the complications which prevent or impede reproduction it is extremely important to do an adequate diagnostic survey

THE STERILE COUPLE

It is important that the husband and wife be investigated simultaneously Male infertility is primarily responsible for the failure of the wife to conceive in at *least* one third of the couples who have been investigated *In another third of these couples* decreased fertility in the male is a *contributing factor It is of no great value* to demonstrate that there are no obvious impediments to conception in the woman who is usually the one first consulting a physician only to find at a much later time that *her mate is sterile*

In order that reproduction can take place the organs must be sufficiently normal anatomically to allow meeting of the sperm and ovum and implantation of the fertilized ovum in the uterine cavity Pituitary ovarian physiology must be normal so

charged or considered cured until another forty eight hours without fever have elapsed following cessation of the anti biotic therapy Under aseptic conditions the introduction of a swab stick through the cervical canal into the uterine cavity serves a double purpose in the treatment of these cases Material can be obtained for examination by smear of the character of the offending organisms or for purposes of culture At the same time the procedure will serve to remove any occluding coagu lum from the cervical canal or at the in ternal os Drainage which is thereby promoted usually serves to hasten recovery The placing of the patient in a semi upright position and encouragement to move about in bed likewise promotes drain age If signs of pelvic peritonitis develop the patient must be taken off fluids and solids by mouth and treated with paren teral fluids in addition to the antibiotic therapy Failure of some response to peni cillin within twenty four hours a clinical picture of unusual severity or the presence of a predominant flora of the coliform group of bacteria should indicate the need of additional antibiotic therapy in the form of dihydrostreptomycin The usual dosage schedule is an initial injection of 2 Gm followed by 1 Gm four times a day for *five days thereafter*

Fever at the end of the first postpartum week is commonly due to urinary tract in fection Mastitis and thrombophlebitis likewise may manifest themselves at this period, but more often appear a few days later Appendicitis though rare must al ways be kept in mind in any postpartum patient who presents abdominal symptoms

Care at Home

Of prime importance to the patient in completing her puerperal recovery at home is a combination of adequate physical rest a psychologically peaceful environment, and a slowly progressive return to full do mestic duties During her first week at home the patient ideally should do little else than tend to the needs of the new baby and devote adequate attention to the psy chologic needs of the husband and any other children Additional domestic help in the home for the first ten to fourteen days is one of the best remedies that can be ordered Full activity should be delayed for a month to six weeks but there is no logic in not allowing from the first such things as deliberate stair climbing, automo bile rides trips to the theater etc

Shower bathing and shampooing are per mitted freely but tub baths and douching are best postponed, at least for a month *Coitus should likewise be advised against* until after the six week check up visit to the doctor s office

The patient should be instructed to no tify the physician if any fever, soreness and redness of a breast, dysuria or excessive bleeding in the form of large clots or gushing ensues The latter manifestations of late uterine hemorrhage are best treated by immediate hospital admission and curet tage of the uterus

Follow-up Care

There should be a check up examination of the patient at six to eight weeks post partum Particular attention should be paid to the condition of the cervix and local lesions in the form of eversion ero sion or small lacerations should be cauter ized with silver nitrate caustic stick or nasal tip electrocautery Repeated treat ment may be needed so the patient should *be seen at intervals of three to four weeks* so long as is necessary

A retroverted uterus particularly if it seems softer than normal and/or tender upon manipulation should be replaced to a forward position and maintained there for at least a month by means of a prop erly fitted Smith *or Hodge type of pessary*

ure, surgery can be considered The results following salpingostomy in the past have been very poor Recent reports offer a better prognosis because of new technics which have been introduced into this very specialized field Obviously these operations should be reserved for the gynecologic specialist

The uterine cavity and fallopian tubes can be visualized by the introduction of a radiopaque oily preparation such as "iodochloral or lipiodol Fluoroscopically the oil can be seen filling the uterine cavity and oviducts and escaping into the peritoneal cavity Roentgenograms taken immediately following the introduction of the oil and again in twenty four hours will demonstrate uterotubal continuity Repeated pelvic examinations will reveal alterations in the size of the ovaries and the appearance and disappearance of many small follicle cysts Rarely, polycystic ovaries may be associated with menstrual irregularities such as irregular bleeding periods and secondary amenorrhea Stein and his associates have described a syndrome characterized by polycystic ovaries menstrual abnormalities, and infertility They have suggested as therapy wedge shaped resection of these large gonads Before such a procedure is undertaken, the patient should be studied carefully and she should have the benefit of expert consultation

True ovarian neoplasms should be removed surgically However, it is rare that these neoplastic cysts and tumors contribute to the infertility of the individual

Ovulation It is not enough to evaluate the anatomic normalcy of the reproductive organs their function must also be studied Normal ovarian function is the key to normal fertility The gonads not only provide the ova but the developing follicles elaborate the estrogenic hormone which maintains the reproductive organs and develops the endometrium for implantation The corpus luteum which replaces the ruptured follicle following ovulation continues to produce the steroid hormones estrogen and progesterone essential to the development of the decidua, and the implantation and early growth of the conceptus

The woman who has normal regular menstrual periods ovulates during most of her cycles and has normal ovarian function In the individual who has an abnormal menstrual pattern, ovulation may or may not occur Ovarian function can be studied in a number of ways, but the most practical methods are the use of basal body temperature graphs endometrial biopsies and vaginal smears The vaginal smear is a good index of ovarian function, but it requires considerable experience in the preparation and the interpretation of the vaginal cytology Furthermore, it is inconvenient to the patient for it is necessary to obtain a daily preparation An endometrial biopsy obtained at the onset of bleeding will show whether or not ovulation has taken place, for the endometrium mirrors the changes that take place in the ovary While endometrial biopsies are important in the study of sterility, they necessarily reflect changes that have taken place in the preceding cycle

The *basal body temperature* is an index of ovarian activity with a high degree of accuracy The patient is instructed to take her temperature orally immediately on awakening each morning and to record these temperatures on a specially designed graph The characteristic graph prepared by the woman with normal ovarian activity will show a consistently low level of temperature following menstruation and continuing until the midcycle At this time there will be a sharp or a slow rise, and the elevated temperature will be maintained for approximately the last two weeks of the cycle The transition from the low preovulatory level to the elevated postovulatory

that a ripe ovum can be discharged from a mature follicle. Thus, a sterility examination comprises two phases: (1) the demonstration of normal organs and (2) the demonstration of their normal function.

INVESTIGATION OF THE FEMALE PARTNER

A complete physical examination is an important preliminary in a sterility investigation. The potential mother should have no serious systemic disorders which may preclude an uneventful pregnancy. The woman with active tuberculosis should not get pregnant until the infection has been arrested for some time. The patient with organic heart disease may exhibit sufficient evidence of cardiac damage to make a pregnancy at any time an undesirable complication.

Pelvic Examination

The pelvic examination should reveal the anatomic status of the reproductive organs. Abnormalities which are amenable to treatment should be corrected. Lower genital tract infections should be eradicated. Endocervicitis should be treated by medication or cauterization. The endocervical canal is an important segment of the reproductive tract, for it shelters and aids in the transport of spermatozoa into the uterine cavity and fallopian tubes. In some women abnormal secretions from the cervical canal are inimical to the survival of the spermatozoa. Measures directed toward the endocervicitis must not result in cervical stenosis.

Uterus. The size, symmetry, location and freedom of movement of the corpus of the uterus should be noted. Malpositions of the uterus do not necessarily interfere with conception. In 1 of 5 normally fertile women the uterus is retroverted. However, when this organ is fixed in an abnormal position by inflammatory residues or endometriosis, fertility can be reduced. Postural exercises may be advised when the uterus is retroverted; surgery is indicated rarely.

The presence of tumors in the uterus is significant. These neoplasms are *associated* with decreased fertility although they are not necessarily the *cause* of it. Many women have successful pregnancies in the presence of leiomyomata. The removal of these tumors of the uterus is indicated rarely, since most women are more likely to conceive without surgery than following it.

Fallopian Tubes and Ovaries. The fallopian tubes and ovaries should be palpated. Again, normal structures are freely movable and gentle palpation will cause no discomfort. The fallopian tubes provide the ideal locale for the fertilization of the egg in addition to serving as the transport mechanism by which the fertilized ovum reaches the uterine cavity. To carry out these functions they must have patent lumens, a fairly normal mucosal lining and mobility to allow for peristaltic activity during the ovulatory period. Inflammatory disease often alters the oviducts anatomically and functionally so that infertility or sterility results. Partial and total blockade account for at least one third of our sterile couples. Tubal patency can be established by the Rubin test, which involves the passage of air or (better) carbon dioxide gas through the uterus and tubes. Tubal normalcy can be demonstrated by kymographic tracings, which may reveal partial or complete obstruction as well as a lack of normal tubal peristalsis.

The patency of partially closed tubes can be improved by repeated uterotubal insufflations with gas. The procedure should be carried out with great care, and the pressure under which the gas flows into the uterus must be carefully controlled. It is usually advisable to keep gas pressures below 250 mm Hg. Complete tubal blockade is rarely amenable to repeated uterotubal gas insufflations. If the passage of a gas and radiopaque oil demonstrates absolute clos

at intervals before an accurate picture of the male can be obtained

The improvement of male fertility can be accomplished by the same measures directed toward the improvement of ovarian failure Good *nutrition* exercise, optimum weight, and a good state of health are reflected in an improved seminal fluid picture Recently there has been some enthusiasm for the treatment of oligospermia by androgens This hormone suppresses spermatogenesis, but a rebound occurs some time following the cessation of treatment It is too early to know whether irreparable damage can be caused by androgens and whether the rebound in spermatogenesis is associated with increased fertility

Every male in whom a marked decrease in fertility has been demonstrated deserves the benefit of expert urologic study

Psychosomatic factors play an important role in human fertility Frigidity, dyspareunia, the inability on the part of the male to complete the sex act satisfactorily, etc., may have their origin not in organic disease but in repressions, fixations, sex trauma, or faulty sex education Previous sex experiences may have left an indelible impression which interferes with the normal sex function The family physician may serve his patient best by a painstaking *study of both partners, toward the end of* helping them achieve normal sex function Sometimes he may need the help of the psychiatrist in unraveling the problem

Abnormal Bleeding in the Menopausal and Postmenopausal Periods

THE most important part of the management *of abnormal bleeding in the menopausal and postmenopausal periods* is the establishment of a correct diagnosis No definitive therapy is indicated until the cause of the bleeding is certain No symptomatic treatment is warranted which may *interfere* with or mask the diagnosis *

CANCER OF THE UTERUS

There is only one symptom that is of any importance in cancer of the uterus *bleeding out of the normal pattern* In the patient who is having regular menstrual periods, bleeding, or spotting between periods, a pinkish discharge or bleeding on contact (*coitus*, douche, examination) is significant Prolongation of the menstrual flow and an irregularity in the cycle should be investigated thoroughly

* See Chapter 28

Any gross irregularity in the menstrual *pattern at the time of the climacteric must* be explained and not ascribed to the 'change of life' Bleeding between the periods, a serosanguineous discharge following coitus or a douche, may mean uterine cancer Any bleeding however slight in the postmenopausal period means cancer of the reproductive organs *unless this* can be ruled out

Other symptoms of cancer of the uterus occur so late in the course of the disease that they are valueless for the recognition of cancer sufficiently early so that therapy offers a good prognosis Purulent discharge *is the result of infection* and necrosis of rather extensive lesions of the cervix Pelvic pain means widespread parametrial extension Loss of weight and cachexia are terminal complaints and bode ill for the patient

plateau marks the period of ovulation It is not possible to identify a fixed point on the rising curve that can be accurately defined as the time of ovulation However, ovulation can be limited to a period of twenty four to forty eight hours Usually the temperature falls twenty four to thirty six hours prior to the onset of the menses but if a pregnancy has occurred the corpus luteum activity, which provides the ther mogenic agent continues and the elevated temperature level is maintained

Basal body temperature records have pro vided other useful information for the study and management of sterility They provide a record of the sex habits of the couple, which is an important factor in fertility Too frequent intercourse may de crease even normal fertility and the mere curtailment of this practice may result in conception In some couples where the hus band has an impairment of spermatogene sis the limitation of coitus to that period when the temperature changes from its low level to its high level may result in an increased number of spermatozoa made available at the critical time of ovulation

Ovarian failure manifested by grossly ir regular menstrual periods, long periods of amenorrhea and an absence of ovulation is difficult to treat In some patients the an terior lobe of the pituitary gland is at fault because it does not provide a sufficient amount of gonadotropic hormones to stimulate its target organs, the ovaries In other women constitutional factors may be the underlying cause An excellent ex ample of the latter is the wartime amenor rhea which developed in so many women who were confined in concentration camps and developed severe malnutrition Many did not menstruate for three or four years but resumed normal ovarian function fol lowing an improvement in their nutri tional state

Although no definitive therapy for ova rian failure is available, much can be done to improve the function of the gonads and thereby increase fertility The obese indi vidual should be placed on a suitable regimen to achieve an ideal weight * Exer cise is as important as a good nutritional state A basal metabolism should be ob tained and in those patients who have a subnormal rate adequate thyroid therapy may be very effective Other therapeutic measures and endocrinal preparations have not been found useful Measures sug gested by others include irradiation therapy of the ovaries or the hypophysis, small amounts of estrogenic hormone in an at tempt to stimulate pituitary function, and the several gonadotropic preparations available commercially

INVESTIGATION OF THE MALE

It is obvious from the foregoing that the male partner merits an equally complete investigation This phase of the infertility study has not received the emphasis that it deserves

In most sterility clinics the semen is in vestigated thoroughly The spermatozoa are counted Abnormal forms are studied and their incidence noted Other constitu ents of the seminal fluid are of importance, for this medium has an important bearing on the survival and fertilizing ability of the spermatozoa

The number of spermatozoa is an impor tant index of the fertility of the individual The normal count may vary from 60 to 200 million per cc Usually the fertility drops rapidly as the count drops below the lower limits The individual who has a sustained sperm count of 5–10 million per cc can be considered infertile but not necessarily sterile In some men no spermatozoa are found in the seminal fluid. As a rule the incidence of abnormal forms increases with the increased severity of the oligospermia It is important to study several specimens

* See Chapter 33

Again the diagnosis is made by the examination of the endometrium obtained by curettage

Ovarian Neoplasms

Ovarian neoplasms benign and malignant, occasionally provoke uterine bleeding The rare granulosa cell tumor is almost invariably associated with a recurrence of bleeding because it produces estrogenic hormones The presence of an adnexal mass will draw attention to the ovarian pathology as a possible cause of the abnormal bleeding

Systemic Diseases

Postmenopausal bleeding is occasionally a prominent symptom in hypertension and vascular renal disease The sudden appearance of vaginal bleeding concurrent with the development of hypertensive disease should raise suspicion of its systemic origin In some women hemorrhage may appear in other vulnerable areas such as the eye However, an absolute diagnosis can be made only after a diagnostic curettage fails to reveal uterine pathology

Vaginal Smears

Vaginal and cervical smears in the diagnosis of cancer of the uterus are used extensively since their introduction by Papanicolaou and Trout The most useful function that they serve is to screen large numbers of women who have no symptoms especially during the years when cancer of the uterus is most frequent When a suspicious or positive cytologic picture is found, the patient is examined carefully, any suspicious lesion of the cervix is biopsied and a curettage done Treatment for cancer of the uterus is almost never instituted on the basis of a cytologic report It is important that a well trained cytologist examine the vaginal smears in order that this procedure be of value

TREATMENT

Cancer of the Cervix

Irradiation is still the sheet anchor in the therapy of cancer of the cervix During the past decade a good deal has been written about the surgical approach to this problem There are few organs and parts of the body which are immune to successful partial or complete extirpation Senescence and the ravages of chronic disease are no longer unsurmountable barriers It is not surprising therefore, that cancer of the uterus which remains confined to the pelvis for a long time should be subjected to renewed surgical exploration

Irradiation will destroy the local cervical lesion effectively and with little hazard to life However it has several real disadvantages There is considerable doubt in the minds of many that it will destroy lymph node metastases Irradiation damage to environmental viscera particularly to the bowel, is a real hazard in spite of the best technic There is always a possibility that deep seated neoplastic cells may survive locally in spite of apparently adequate irradiation

Irradiation therapy has made notable improvements Better methods of radium application as well as physical means to measure dosage more accurately have made it possible to increase total dosage without increasing the hazard to normal pelvic organs New sources of irradiation are being developed Cobalt has been applied locally and it will soon be used for external therapy as roentgen ray sources are used today A great deal of research on isotopes is in progress and these sources of irradiation may become available in the treatment of cancer of the uterus

The end results of therapy of cancer of the cervix are measured in five and ten year cures This means that the patient is alive and apparently free of recurrences at the end of five or ten years However, this yardstick for evaluating the results of

The diagnosis of cancer of the uterus is not difficult to make if its presence is kept in mind constantly A pelvic examination must be a routine part of every physical examination It must include the visualization of the cervix through a speculum and in good light The carcinoma lesion is hard and indurated in contrast to the rest of the cervix The surface bleeds easily on contact The positive diagnosis must always depend on the biopsy of a suspicious area and histologic examination

If the portio of the cervix is smooth and normal in appearance, it is well to probe the cervical canal with a small cotton applicator The examiner must account for bleeding provoked in this manner

If the cervix and cervical canal are normal in appearance and palpation, the patient should have a diagnostic curettage to rule out the presence of an endometrial carcinoma This should be done in a hospital under anesthesia so that the entire uterine cavity can be explored with the sound and curet All tissue obtained should be fixed promptly and sent to the laboratory for a diagnosis Although ovarian neoplasms cause vaginal bleeding rarely, careful pelvic examination should be made to determine the normalcy of all the pelvic organs

Estrogenic Bleeding

The patient who has been receiving estrogenic hormone in any form may have uterine bleeding This may come on the cessation of therapy or during its continued use The medication should be stopped promptly, which should be followed by the cessation of all bleeding within a week If the bleeding continues or if it recurs a prompt diagnostic curettage is indicated

Polyps

A polyp or several of them may be visualized in the cervical canal on speculum examination These usually arise from the endocervical epithelium and are almost invariably benign The small ones may be removed by grasping their bases with a dressing forceps and twisting them off by rotation of the instrument The larger polyps may have to be removed in the hospital Obviously they should be sent to the pathology laboratory for histologic examination If bleeding continues after the removal of a cervical polyp or recurs the patient should have a diagnostic curettage

Endometrial polyps are not uncommon at this period of life and may be associated with small myomas The diagnosis is made at the time of curettage for irregular bleeding at the menopause or bleeding after the menopause The diagnostic procedure will usually stop the bleeding However, if bleeding continues in spite of a curettage or recurs again at a later time hysterectomy should be considered seriously

Erosions

Erosions of the cervix rarely bleed spontaneously or on examination An erosion which bleeds on contact should be biopsied adequately in order to rule out the possibility that it is a squamous cell carcinoma of the cervix

Leiomyomas

Submucous myomas may be so small that they do not alter the size and contours of the uterus These may become necrotic, or they may become dislocated from their environment and cause uterine bleeding A diagnostic curettage during which the uterine cavity is carefully explored will usually reveal the irregularity produced by the nodule

Tuberculosis of the Cervix

Tuberculosis of the cervix is rare, but it may involve the endometrium more often It is almost invariably secondary to tuberculosis of the peritoneum and fallopian tubes or a focus elsewhere in the body

Roentgen ray therapy is designed primarily to deliver irradiation to the tissues lateral to the cervix and to the parametria. It is desirable to deliver to the lateral pelvic walls a tumor dose of 3500 to 4000 r in four or five weeks. There has been considerable doubt whether the primary or iliac group of nodes can be reached by external irradiation. Fletcher has devised an interesting new technique whereby multiple small beams of roentgen rays are directed at these areas in a way that a higher depth dose can be obtained without damage to normal tissues.

Cancer of the Corpus

Adenocarcinoma of the corpus of the uterus is likely to remain a local lesion confined to the uterine wall and its cavity for a longer time than cervical cancer. When extension occurs outwards it may grow in the direction of the cervical canal or fallopian tubes. Ultimately the parametrial tissues and glands become involved so that the enlarging uterus loses much of its mobility. Lymph gland involvement follows the general pattern seen in cancer of the cervix.

Many factors influence the rapidity of growth of the neoplasm, among which are the histologic character of the neoplasm, the age of the patient and the presence of infection. In general it can be said that the more nearly the histologic pattern favors normal glandular epithelium, the slower the progress of the lesion. The highly undifferentiated cellular patterns are often found in rapidly advancing tumors. An attempt has been made to grade corpus carcinomas according to the histologic findings.

Surgical Treatment. Surgery has been the most common method for the therapy of cancer of the uterine corpus. This is due to the fact that this lesion was considered less sensitive to irradiation than cervical cancer and that it remains localized to the uterus for a long time. Neither of these contentions is entirely accurate. In some clinics the patient is first treated with intracavitary radium receiving 3000 to 5000 milligram hours and an operation is done six or eight weeks later. In other institutions surgery is followed by external irradiation. There is little evidence that irradiation before or after surgery increases the likelihood of a cure, although preoperative irradiation in patients who have a large tumor growth will produce a marked regression of the lesion and decrease the hazard of infection.

The increased safety of radical surgery in senescent individuals should lead to more extensive surgery in cancer of the corpus. The operation should include the removal of the reproductive organs as widely as possible including a liberal cuff of vagina and pelvic node dissection such as is carried out today in cancer of the cervix. Such complete procedures will increase the five-year cure rate from the present 65 per cent, which is far too low in this favorable malignant lesion.

Management of the Advanced Cancer Patient

The medical care of the patient with progressive cancer of the uterus is not an easy task. Irradiation should be used to stay the progress of metastases, although the ultimate outcome is inevitable. Symptomatic treatment should keep the patient as comfortable as possible.

It is well to discourage the patient from taking to her bed and to keep her ambulatory as long as possible. To this end the early use of narcotic drugs should be discouraged. Mild analgesic drugs may provide relative freedom from pain.

The necrotic ulcerative lesions in the vagina may be less offensive if a daily douche is administered. Bladder infection may be combatted by the use of one of the sulfonamides.

Eventually morphine or one of its deriv

therapy is not entirely satisfactory for there is an increasing number of women who have been treated so successfully that they are free of malignant disease for ten years but eventually succumb from the original neoplasm

The cure rate varies with the extent of the lesion at the time treatment is first instituted An early localized carcinoma of the cervix without extension to adjacent areas Stage I will show a five year cure rate of 70 per cent if adequately treated by irradiation (Radiumhemmet) On the other hand this good result drops to 51 8 per cent in Stage II where the neoplasm has extended to the tissues about the cervix and the parametria although superficially it is still a cervical lesion

In the several clinics where some patients with Stage I or II cancer of the cervix are subjected to radical surgery the results compare favorably with those obtained by irradiation Thus Meigs feels that the mode of therapy in these patients is a matter of choice for the individual who is to care for the patient However the very obese or the very old patient with diabetes or heart disease is a poor risk for extensive surgery and is better treated by irradiation

Advanced carcinoma of the cervix with local extension to the vagina and lymph node metastases is difficult to treat by irradiation or surgery The progress of the neoplasm locally can usually be arrested by irradiation However the metastases in local and distant lymph glands are difficult or impossible to destroy by radium or x ray It is in these patients that Brunschwig has advocated mass resection of the pelvic organs including the removal of the environmental viscera that are involved in the neoplastic process He has removed the bladder and rectum and implanted ureters in the bowel thereby stripping the pelvis clean of all structures and tissues which might harbor malignant cells Unfortunately, most of these patients who have a complete pelvic exenteration operation have distant metastases which cause death in a short period However, a limited period of survival in a fair degree of comfort may justify such radical procedures and a rare patient may be cured of her fatal disease

Irradiation Therapy It is not the purpose of this discussion to describe the technical phases of irradiation therapy * However some general observations may be pertinent Effective irradiation therapy requires the cooperative efforts of the gynecologist, the radiotherapist and the physicist It is a precise method of treatment and requires no less skill than radical surgery The average lethal irradiation dose for carcinoma cells is known but it is difficult to determine the extent of the lesion so that it may receive adequate irradiation Furthermore, it is even more difficult to safeguard normal tissues from extensive destruction

Radium and roentgen ray therapy are usually combined in various ways Roentgen ray therapy is often used preliminary to the intracavitary radium treatment in the presence of grossly ulcerating cervical lesions with infection In these patients external irradiation will favor some regression and healing of the local lesion and reduce the hazard of infection Small lesions confined to the cervix are usually treated first by radium

The amount of intracavitary irradiation varies considerably The whole length of the uterine canal is treated by tandem applicators although most of the radium is applied to the cervix and the vaginal vaults by various applicators which are designed to distend these vaults and bring the radium as close as possible to the bases of the parametria In the Stockholm technic three different applications of radium are used at weekly intervals and the patient will receive a total dosage of 6000 or 8000 milligram hours

* See Chapter 46

This is *not* a yeast These fungi produce symptoms only when sufficient carbohydrate material is present in the vagina—nearly always *in pregnancy* or after estrogenic therapy in the menopause The diabetic woman may have vulvar mycosis especially when the diabetic condition is uncontrolled Thus *C albicans* is of importance only when it produces pruritus one invariable and usually major complaint The untreated pregnant patient s symptoms disappear almost immediately *within two days after delivery*

Candida albicans produces caseous like material in the vagina or thrush spots (small white plaques) on the vaginal walls Mycotic vulvitis produces an acute redness and hyperemia with not uncommonly a slight bluish tint The numerous breaks on the labia are the result of scratching *If the condition becomes more protracted the reaction spreads beyond the hairline*

Diabetic patients with high renal thresholds may not have typical results from urinary tests Thus a glucose tolerance test* may be necessary to exclude or include the diagnosis when vulvitis is associated with pruritus and the typical appearance of mycosis

An aqueous or a glycerine vehicle containing 1 per cent gentian violet has long been reliable therapy An *occasional* individual becomes sensitive to gentian violet and has severe chemical vaginitis and vulvitis Dilute Lugol s solution can be used in place of the gentian violet

For over two years we have been using with excellent results a preparation in a tragacanth acacia jel containing 3 per cent ricinoleic acid and 0 5 per cent oxyquinoline sulfate (aci jel) It does not cause stain irritation or other undesirable features The medication is placed in the vagina each evening by means of a suitable applicator Propiongel ' is an alternative

Special anal hygiene should be employed to avoid the introduction of these fungi from the bowel It is important to treat the pregnant patient so that the baby will not acquire oral thrush from contamination during delivery or shortly afterward The *diabetic should have the diabetic state* controlled and the local process treated simultaneously

* See Chapter 49

VAGINAL TRICHOMONIASIS

Vaginal trichomoniasis is one of the two most common causes of discharge excessive cervical secretion is the other

The discharge associated with trichomoniasis is *characteristically yellow bubbly* or foamy has a putrid odor, and may be accompanied by vulvar irritation and introital pruritus The perineum may also have some irritation The trichomonads which are found on microscopic examination of a hanging drop or moist saline preparation are slightly larger than white cells and somewhat elongated Their *movement distinguishes them further from* epithelial fragments and leukocytes and the diagnosis can be established beyond doubt with observation of the active flagella, four anteriorly and one posteriorly

The vagina is stippled or spotted in very acute situations especially in the upper vagina or around the cervix *The latter not* uncommonly has a rather thin watery type *of discharge not unlike* that of acute rhinitis

The vaginal involvement can be treated with plain lactose tablets or beta lactose in No 12 veterinary capsules One capsule should be inserted into the vagina each evening Some watery secretion results from hydroscopic action *Although lactose is not fermented by C albicans* an occasional patient may develop mycosis Douches should be avoided during this therapy except for perhaps a weekly douche of one quart of plain water or one containing two tablespoonfuls of vinegar

atives are the only drugs which will keep the patient comfortable and allay some of the mental anguish associated with a hope less disease In some patients the intrac table pain in the pelvis back and lower extremities can be relieved effectively by chordotomy

Endocrinal therapy has not been success ful in the treatment of cancer of the uterus although androgens are used oc casionally

The patient with terminal cancer is a difficult problem for her family and her doctor The kind considerate medical attendant can do much to make the last days more tolerable and in a measure he will compensate for our inability to learn the cause and the cure of this dread disease

Lower-Tract Pelvic Infections

CERVICITIS vulvitis and vaginitis the common lower tract pelvic infections mani fest themselves by offensive discharge (leukorrhea) and the consequences thereof The discharge may be copious or may be noticed merely as a scant stain on the pa tient s undergarments There may be an obvious foul odor At times the irritative consequences of discharge alone comprise the presenting symptomatology pruritus vulvar burning dysuria and frequency dyspareunia etc

CERVICITIS

Treatment of cervicitis is directed toward eradication of infection and correction of structural abnormalities These include erosion eversion lacerations cystic disease polyps and stenosis Mild infections asso ciated with superficial lacerations or ero sions occasionally can be eliminated with bactericidal agents topically applied Among these are iodine tincture U S P negatan and silver nitrate solution 20 per cent Sulfonamide suppositories or ointments may be helpful if organisms are involved which are susceptible to the drug locally applied Lactose is used in the vagina to lower the pH of vaginal secre tions encouraging growth of an acid flora which inhibits pyogenic organisms Douches with vinegar solution one or two table spoonfuls to a quart of water provide an other means of acidification

Deeper cervical infection usually requires coagulation treatment or cauterization Lunar caustic stick may be given a trial though electrocauterization through a nasal tip is usually more effective To prevent stenosis no more than one third of the circumference of the endocervical canal and adjacent vaginal face should be treated every two weeks These steps should not be taken in the presence of acute infection

If one discovers a clearly purulent dis charge from the endocervix in the presence of marked congestion of the portio gonor rhea should be suspected and smears and/or cultures of the discharge obtained for gram staining Milking of the urethra and palpa tion of the Bartholin s glands may be help ful *

Any cervical lesion which bleeds upon palpation sponging or light trauma with the speculum should be suspect of malig nancy Investigation of the lesion with smears for cytologic study and/or biopsy is at once in order

MYOTIC VAGINITIS AND VULVITIS

Vaginal and vulvar mycosis is caused by a fungus known as *Monilia* (usually *albi cans*) but also called *Candida* (*albicans*)

* See Chapter 40

Upper Tract Infections (Pelvic Inflammatory Disease)

PELVIC inflammatory disease commonly called P I D is a clinical syndrome usually composite produced by upper genital tract infection and involving—by various degrees—the uterus and tubes and frequently the ovaries and pelvic peritoneum The nongonorrheal types usually present involvement of the lymph channels and connective tissue at the bases of the broad ligaments

Acute and chronic stages of the syndrome are recognized though there are often seen intermediate (subacute) phases frequently in the form of exacerbations of a chronic state

The three common etiologic types are gonorrheal postabortal and postpartum The latter is most common at the present time over the country as a whole Other cases have their origins in operations for appendicitis or noninfective pelvic disease curettage, and other instrumentation of the uterus tubal patency tests cervical treatments of various kinds and tuberculosis

ACUTE PELVIC INFLAMMATIONS

The diagnosis and management of acute postpartum pelvic infection is discussed in Chapter 31 Tuberculous disease of the pelvis does not have a true acute phase Gonorrheal postabortal and other etiologic types differ little from each other in well developed cases and diagnosis depends basically upon history plus bacteriologic investigation in the forms of smears and cultures

Pelvic examination will reveal exquisite tenderness on both sides of the uterus and when the latter organ is moved by manipulation of the cervix This peritoneal tenderness with resistance and spasm of the abdominal muscles may prevent palpation of parametrial or adnexal masses swollen tubes as such and perhaps even the uterine corpus In cases when attempts at abortion have been made the uterus may be large and boggy, with the cervix open or closed in accordance with the stage of the abortion Blood clots within the cervix may help to differentiate abortion from a menstrual period which so frequently accompanies or precedes the development of gonorrheal salpingitis The lower tract infection may still be present in the specific form of the disease or may have existed as long as weeks or months before Endocervical discharge may contain gonococci Where the acute episode represents an exacerbation after a period of chronicity the original source of the process may be obscure in the absence of a reliable history

Appendicitis, ectopic pregnancy and ruptured or twisted ovarian cyst must be considered in differential diagnosis Acute inflammation usually makes itself obvious by its bilateral location relatively high fever and white blood cell count, and the antecedent history

Prompt therapy with penicillin or other antimicrobial agents will cure the disease before abscesses develop If treatment is adequate the chances of tubal occlusion with resultant sterility are greatly lessened however, the possibility of ectopic pregnancy may be enhanced Acutely ill patients usually require pain relieving drugs and fever measures Fluids should be administered intravenously if the oral intake is inadequate Copious hot douches are of benefit in some cases

Seldom is difficulty encountered in keeping the patient in bed The head should be elevated and the feet lowered A board should be placed against the foot of the bed so that the patient takes pushing up exercises thereby providing dependent

to prevent an excessive accumulation of lactose in the vagina.

The trichomoniasis will require treatment for at least four to six weeks, depending upon the extent of inflammation. In severe or chronic cases the inflammatory reaction may extend under the vaginal mucosa. This state accounts for the need for protracted therapy until healing is complete. Otherwise recurrence is likely.

Focal sites in the cervix, in the form of cervicitis, erosion or eversion, may contribute to recurrences. A chemical cautery, such as silver nitrate in either 20 per cent solution or the form of lunar caustic stick, should be used as initial treatment in such instances. Increased discharge will follow and perhaps some bleeding but the hazard of pelvic cellulitis will be greatly reduced. After one or two such treatments electric cautery may be used.

Sometimes repetition is necessary after one or two months. If the vaginal condition fails to clear or recurs, a thorough urethroscopic and cystoscopic examination may be advisable. Urinalysis alone will not reveal the presence of some contributing lesions in the urethra and bladder. One need not find actual trichomonads to incriminate a contributing source, but any urologic lesions should be treated appropriately. The husband should use a condom at intercourse during therapy to prevent intermittent reinfections.

POSTMENOPAUSAL VAGINITIS

Postmenopausal vaginitis is moderately common and is recognized by signs of inflammation superimposed upon an atrophied vaginal mucosa. Diethylstilbestrol daily in 0.5 mg amounts by mouth will give quick relief. After six weeks of treatment the dosage may be gradually reduced over the next six weeks. When the condition is a nonspecific vaginitis or trichomoniasis, estrogen therapy will give equally good results in the postmenopausal patient. The use of oral diethylstilbestrol is simple, economic, and more convenient than the vaginal suppository form.

Douches should be avoided except as stated under "Trichomoniasis" because they do not get at the base of the trouble. Acid douches affect the pH only temporarily. Alkalis should at no time be used, since hyperacidity of the vagina does not exist.

CHILDHOOD VULVOVAGINITIS

Vulvovaginitis in the child is similar to postmenopausal vaginitis in its physiologic and pathologic pattern. Gonorrheal infection is not nearly as common now as in the past, but a child is prone to become infected very early if others about her are so infected. The child may likewise have urethritis and cervicitis.

Parenteral penicillin, in adequate dosage according to age and weight, and given over a forty-eight- or seventy-two-hour period, is treatment of choice in these cases. Results are almost uniformly excellent. In the occasional case, particularly where there are secondarily invading bacteria not susceptible to penicillin, one may resort to adjuvant therapy in the form of estrogenic hormone. The effect of estrogen is to bring about temporary maturation of the vaginal mucosa to an adult type, thereby rendering the tissues nonsusceptible to the infective organisms.

Estrogen therapy in these instances is conveniently given in the form of orally administered diethylstilbestrol, 0.2–0.3 mg daily. Treatment should continue for approximately three weeks. During treatment the child may complain of mammary tenderness, and a mucoid vaginal discharge from stimulated cervical glands likewise may be present.

pation to one of a sedentary nature Mild sedation as well as antianemia and vitamin supplement therapy *may be necessary*

Heat to the pelvis *can be given in the* form of long hot vaginal douches at least *daily with the exception* of the menstrual *period* A minimum of two quarts of as warm as tolerable tap water must be used with two or three tablespoonsful of distilled vinegar added *The douche is best* taken in a semirecumbent position within *a bath tub Heat to the pelvic organs can* be applied by means of an Elliott machine or diathermy apparatus Three or four treatments a week for three or four months may aid in alleviating the discomfort

Should a flare up of acute pain, fever, and leukocytosis develop in the course of heat therapy, the latter must be stopped and the patient treated as an acute case If the symptoms alluded to at the beginning of this discussion subside completely, the patient may gradually be taken off her strict regimen Where infertility is of *great* concern to the patient tubal patency studies must not be done for at least six months after the *pelvis is entirely quiescent*

Surgery

If several months of intensive medical treatment conscientiously carried out does not produce adequate amelioration of symptoms, or if the patient s condition is handicapping her in her attempts to main*tain an* occupation, surgery must be resorted to No surgery should be undertaken in a period of flare up Surgery must *be thorough* in every case of bilateral pelvic inflammatory disease This implies *total hysterectomy* and bilateral salpingo oophorectomy Attempts to leave a residuum of involved tissue to forego inducing the menopause are not profitable, and invariably result in continuation of distressing pelvic symptoms requiring re operation *The patient should be acquainted with* these facts and told that estrogen substitution therapy can suppress successfully the so called change of life symptoms after radical surgery

TUBERCULOUS PELVIC INFLAMMATORY DISEASE

Tuberculosis of the pelvic organs is almost invariably secondary to tuberculosis in some other part of the body* *Active tuberculous salpingitis and pelvic peritonitis* have been treated successfully with streptomycin and *p* aminosalicylic acid The general management of tuberculosis should be instituted Surgery is occasionally indicated late in the disease when the process in the pelvis has become quiescent When surgery is contemplated it should be directed toward the removal of all of the reproductive organs

* See Chapter 16

Endometriosis

ENDOMETRIOSIS is the disease of ec*topic endometrium* a spread to other anatomic locations of glands and/or stroma normally lining the uterine cavity Most common of these ectopic sites are the myometrium (see *Adenomyosis*) ovary, tube and peritoneum covering the entire posterior pelvis In addition to such regional involvement the discrete lesions or endometrioma are found in more remote locations such as rectum bladder small bowel appendix perineum thigh umbilicus lung arm and lymph nodes

Benign endometrium may spread by di

drainage and decreasing the chances of intravascular clotting in the leg and pelvic veins

Constipation should be prevented Heat or cold may be applied to the abdomen The antibacterial agent should be administered until the patient has been free of fever for at least forty eight hours

After the initial diagnostic vaginal and pelvic examinations further examinations are made *only* if indicated as when abscess is suspected

If at the time of admittance, the diagnosis is either acute P I D or ruptured appendix or diverticulum, culpocentesis is performed In some instances a ruptured tubal pregnancy is mistaken for P I D The introduction of a needle into the cul de sac of such patients proves the diagnosis Tubo-ovarian ovarian or other pelvic inflammatory processes which do not respond to antibiotics—usually because administration is too late—and proceed to the formation of abscesses should be drained via the posterior vaginal fornix if practicable or extraperitoneally if such an approach is preferable

When the acute process has been caused by abortion and the latter is in an incomplete phase it is more prudent for the practitioner to defer curettage and give blood until sepsis has subsided—unless bleeding threatens the patient s life If there is any inkling of criminal induction in history or findings prophylactic antiserum therapy against tetanus and gas gangrene should be given Pelvic thrombophlebitis is another complicating condition most common in postabortal cases *

Patients of low intelligence sometimes fail to take care of themselves and so have recurrent attacks of acute salpingitis Often they acquire new gonorrheal infections They should be treated as if having an initial attack of P I D

* See also Chapter 12

CHRONIC PELVIC INFLAMMATORY DISEASE

Patients may be encountered who show evidence of having had acute infections but who do not exhibit any active inflammation, either bacteriologically or clinically Among their disorders may be immobile retrodisplaced uterus frequently with prolapsed fixed ovaries giving rise to dyspareunia, menstrual disorders from ovarian dysfunction, abdominal pain caused by adhesions, sterility, and urinary or rectal symptoms or both resulting from a cystic mass in the pelvis

Medical Management

The medical treatment of chronic pelvic inflammatory disease is nonspecific, unspectacular, and very often unsuccessful From the patient it demands understanding of what can be accomplished knowledge of the consequences of surgical treatment and a desire to be wholly well that is strong enough to produce complete cooperation through months of adherence to a strict regimen The physician must be encouraging though firm in his management of the patient s complaints and he should turn away from the temptation of surgery until medical treatment has been thoroughly tried

The crux of medical treatment in this condition is a combination of rest for the pelvic organs with local heat therapy Pelvic rest implies very limited sexual activity at any time, with complete abstinence several days before and after menstrual periods Alcohol and other stimulating factors are forbidden Pelvic congestion is further decreased with proper bowel management consisting of low residue diet and nightly mineral oil (15–45 cc) At the time of menstruation general body activity must be curtailed to the point of 'semi invalidism' and definitely limited at all other times of the month This may mean changing the working woman s occu

sis is also possible through identification of small blueberry spots on the surface of the ovaries or pelvic peritoneum during the course of operations for other pelvic disorders

Without visualization there is no classical diagnostic formula even for extensive pelvic endometriosis In the absence of a history of pelvic infection endometriosis should be suspected if the ovaries are adherent, if there is a tender mass in the cul de sac if a retro-displaced uterus is adherent if there is nodulation along the sacrouterine ligaments or if upward pressure against the cervix causes pain Recto*vaginal examination is most valuable with* search for point tenderness or nodules of variable size Examination must be made on the day of onset of menses or the day before An enema should precede examination The pain of endometriosis is apt to be intensified by heat On the other hand the pain of pelvic inflammation is usually diminished by hot douches Since androgens tend to relieve the pain of endometriosis the male hormone may serve as a diagnostic aid In most instances surgical exploration is necessary to establish an ab*solute diagnosis and to obtain an estimate* of the degree of pelvic involvement

TREATMENT

Surgery

Surgical removal of the ovaries or their destruction by radiation is followed by prompt regression atrophy *and fibrosis of* the lesions of endometriosis However the trend in recent years has been toward more conservative treatment Castration is advised only in women who are in the menopause and in patients in whom there is serious involvement of the intestine bladder or ureter Under the latter circumstances it may even be advisable to forego the risk of a mutilating surgical procedure by employing radiation to effect castration

In women who are in the child bearing age preservation of the ovaries and of the *child bearing function is of utmost* importance At this time, therefore the importance of prophylaxis against endometriosis and the importance of early recognition of the disease is being stressed Early exercise of the child bearing function is regarded by some as the most effective means of reducing the incidence of endometriosis Surgeons should recognize the importance of searching for, recognizing *and extirpating early nonsymptomatic le*sions during the course of operations for appendicitis or for the relief of other pelvic disorders

Except where definitive surgery is mandatory, the surgeon s efforts should be directed toward the salvaging of ovarian tissue freeing and suspending *the uterus* establishing tubal patency and puncturing and destroying only those lesions which are readily accessible After such conservative surgery, the physician must depend upon pregnancy and/or hormone therapy for the suppression of further activity in the lesions and for the control of subjective symptoms If such conservative measures should prove ineffective, resort to radiation *for the destruction of residual ovarian tis*sue will afford assurance of relief

Hormonal Treatment

Pregnancy is probably not only the best assurance against endometriosis but also the most effective means of arrest and even *cure of existing endometriosis* However the male and female sex hormones too may be employed to afford subjective relief and to arrest the progress of the disease They may enhance the chances for conception and even effect complete regression and fibrosis of extensive lesions

Diethylstilbestrol Karnaky endeavors to suppress ovulation and menstruation by administering ascending massive doses of diethylstilbestrol without interruption over a period of many months Under this

rect invasion of the myometrium and of the endosalpinx by exfoliation of cells through the fallopian tubes with implantation on the ovaries and peritoneum by lymphatic metastasis to lymph nodes, by hematogenous metastasis locally and to such distant organs as the kidney and lung This theory of benign metastasis seems to account for the origin and spread of endometriosis better than does the theory of congenital coelomic metaplasia However the latter is difficult to disprove as the origin of endometriosis in any patient The trigger mechanism that initiates the spread has not been isolated

Endometriosis may be found in women of all ages after the menarche but occurs most frequently in the middle and late twenties through the early and middle thirties Endometriosis is most common in those patients who have had a long period of uninterrupted menstrual periods as in women who marry late or who delay pregnancy following marriage by means of contraception

PATHOLOGY

The early lesions of endometriosis appear as minute red or bluish spots which are most likely to be found on the surface of the ovaries or on the peritoneum of the cul de sac As these lesions develop and enlarge they penetrate and invade subperitoneal tissue layers Bleeding occurs into the lesions and causes the formation of tarry chocolate cysts Rupture of these cysts with spillage results in a chemical peritonitis which leads to the formation of the characteristic dense fibrous adhesions that glue together, distort and constrict the structures which occupy the pelvic cavity

SYMPTOMS

Pain is the only constant symptom of endometriosis The degree of pain, however is no index to the extent of the disease The intensity of pelvic discomfort related to endometriosis is characteristically increased by menstruation This may simply take the form of an acquired dysmenorrhea or an alteration in the type of pre-existing dysmenorrhea The menstrual backache may extend to the thigh or to one leg Low, deep pelvic discomfort induced by jarring, walking downstairs, riding, etc, is characteristic Acquired dyspareunia, if of the deep or penetration variety, may be significant Symptoms may be related to the location of the endometriomas upon large or small bowel The disease should be suspected if the patient complains of rectal pain but harbors no demonstrable intrarectal pathology This pain may be manifested along with the bowel movement or with the passage of gas, especially with a menstrual period or only with a menstrual period Superficial implants on the rectum may cause diarrhea with a period There may be lowgrade intestinal obstruction manifested by nausea cramps and vomiting at the time of the menstrual period, or constipation—sometimes to the point of severe and absolute obstipation Bladder implants may be manifested by irritability of the bladder at the time of periods, or even frank hematuria Menorrhagia should be regarded as symptomatic if the bleeding is accompanied by pain The appearance of a symptom complex, or palpatory findings of pelvic inflammatory disease after 35 years of age is usually endometriosis, since pelvic inflammatory disease becomes much more rare after 35 years of age Unexplained infertility in the presence of any of the above symptoms should be regarded as endometriosis until proven otherwise

DIAGNOSIS

A diagnosis of early, nonsymptomatic endometriosis is frequently established through recognition of the typical bluish, cystic lesions in the vaginal vault during routine pelvic examinations Early diagno-

Diagnosis

The symptoms of adenomyosis per se are very difficult to ascertain because the lesion is also often associated with other pathologic conditions of the pelvis which may cause similar complaints Excessive, irregular uterine bleeding is the most common complaint followed by dysmenorrhea and other types of pelvic discomfort The diagnosis of adenomyosis as the principal pelvic disease is rarely made by examination of the patient before operation and not infrequently the diagnosis is missed until the extirpated uterus is examined by the pathologist If fibroids are limited in number and associated pelvic pathology of the adnexae is not overwhelming adenomyosis mav be suspected in a uterus which is somewhat enlarged and irregular, from various sized raised areas or lumps in the uterine wall proper, from softening of the organ as a whole and of the lesions specifically in the free interval between menstrual periods and by the tenderness of myomatous masses at or just before a menstrual period

Treatment

Ideal and definitive treatment is surgical This implies complete hysterectomy and concurrent removal of all pathologic tissue in every case, and most likely bilateral salpingo-oophorectomy in any patient at or after 40 years of age Where operation is a very serious risk for the patient relief of symptoms may be obtained by castration through roentgen ray therapy or properly carried out radium implantation into the uterus These treatments are contraindicated in the presence of moderate or marked pelvic inflammatory disease with any activity or history of recent activity Temporarily, short term amelioration of symptoms and some shrinkage of the lesions may be produced by testosterone As in endometriosis externa dosage should be adequate to inhibit menstrual periods

Uterine Myomas (Fibroids)

THESE most common of the benign pelvic tumors are composed of smooth muscle cells and variable amounts of fibrous connective tissue The amount of the latter determines their firmness which in turn has given rise to the misnomer fibroid The original source of these new growths is in dispute but is either the wall of uterine blood vessels or unripe uterine muscle cells The trigger mechanism in their histogenesis is some unknown hormonal process involving estrogen and/or progesterone

Symptomatic myomas are most common in women between 35 and 45 years of age who have not been pregnant Among Negroes they are seen more frequently than in whites and at an earlier age In size these tumors range from the microscopic to masses weighing as much as 40 pounds multiple tumors are the general rule

According to location myomas may be entirely within the uterine wall (intramural or interstitial) but they are prone to point through one or the other surfaces (subserosal or submucus) In either of these locations they are commonly pedunculated the intracavity type occasionally appear at or through the cervical os into the vagina Less common locations are the body of the cervix and between the leaves of the broad ligament (interligamentary) Rarely they may lose their attachments to the uterus and become wandering or parasitic tu

treatment his patients have experienced marked relief of pain and Karnaky reports that he has observed definite softening of the pelvic mass and restoration of uterine mobility Some of his patients have experienced no further menstrual pain for as long as nine years, and in a series of 37 patients so treated 5 have become pregnant We have used 100–200 mg diethylstilbestrol on 4 patients with good results in 2 and fair in the other 2 over periods of four to six months

In a smaller series of patients Bickers reported equally gratifying results without the massive uninterrupted dosage of diethylstilbestrol employed by Karnaky Bickers endeavors only to suppress ovulation and he permits cyclic withdrawal bleeding He recommends 5 mg of diethylstilbestrol daily from the fifth to the twenty sixth day of each menstrual cycle

Androgens Androgens may be employed to good advantage in the conservative treatment of endometriosis Patients with extensive pelvic involvement have experienced gratifying symptomatic relief under androgen therapy Painful nodules in the cul de sac and in the rectovaginal septum have been observed to regress and atrophy, leaving only small painless fibrous areas Objections to the use of androgens are based solely on the masculinizing potential of the testicular hormone It should be emphasized here that in treating endometriosis the desired physiologic influence of the male sex hormone can be accomplished with a moderate dosage, well below that which would induce masculinization Usually 25 or 50 mg in oil injected weekly is adequate

Satisfactory management of endometriosis requires meticulous study and good judgment on the part of the physician and understanding and cooperation on the part of the patient The patient should be made to understand why the physician is reluctant to employ radical treatment involving castration with all its unhappy implications She must be made to understand and appreciate the surgeon s efforts to conserve ovarian tissue and the reproductive function even at the risk of some future trouble

Adenomyosis of the Uterus

ADENOMYOSIS has also been called endometriosis interna, since it is characterized by the presence of ectopic or aberrant endometrium within the myometrium of the uterus itself The lesions islets of endometrium, find their way into the myometrium by a downgrowth from normally located glandular tissue To be classified as true adenomyosis the endometrium must be deeply located in the myometrium since it is a normal deviation to find minimal downgrowth of glands in practically every adult uterus

By far the greatest number of cases of adenomyosis of the uterus occur in the fifth decade of life some 10 to 15 years later than the peak age of incidence in external endometriosis Some relationship to uterine fibroids (fibromyoma) may exist, since these tumors are found in association with adenomyosis in from 30 per cent to 80 per cent of cases The basic relationship may be hyperestrinism inasmuch as both entities commonly are found in patients having anovulatory cycles with endometrial hyperplasia or sustained early nonsecretory endometrium Pelvic inflammatory disease and ovarian follicular cysts may be present in many patients

gree of certainty myomectomy may be a helpful procedure The operation is best done abdominally for the usual subserous or intramural tumors, but submucous pedunculated growths require the vaginal route

Symptomatic Treatment

Despite the presence of large or small new growths myomas of the uterus in many instances may coexist with completely normal cyclic endometrial changes By the same token myomas may exist in a uterus whose endometrium undergoes grossly abnormal structural changes which are entirely independent of the presence of the tumors and entirely under the control of abnormal ovarian function Most common is hypermenorrhea (menorrhagia) with endometrial hyperplasia induced in the course of anovulatory cyclic ovarian function The myoma or myomas may play a part in the patient's hypermenorrhea in the face of endometrial hyperplasia by creating poor myometrial contractility

Numerous symptomatic measures have been proposed to establish normal tone in the uterus together with normal ovarian function Improvement in myometrial contractility may come simply from improving the patient's general health and nutritional status with particular emphasis on protein intake as well as mineral and vitamin regulation Asthenic patients occasionally benefit remarkably from a diet rich in fats and carbohydrates as well as vitamins Conversely, weight reduction may greatly improve the functions of the uterus and ovaries as well in the obese patient Thyroid extract when indicated is often of great assistance From the standpoint of poor contractility alone, treatment with oral ergonovine maleate preparations may be effective

If general systemic and metabolic measures do not achieve success in curbing the hypermenorrhea specific hormone therapy may be tried As indicated in the section on abnormal uterine bleeding hormonal therapy may take the form of estrogenic substances, progesterone, or androgens alone or in combination Treatment with a potent luteinizing preparation such as human chorionic gonadotropin, theoretically would seem to be effective in anovulatory type of endometrial hyperplasia but results are often disappointing

Curettage of the uterus is indicated early in any program for treatment of hypermenorrhea in the presence of myomata The curette is the only diagnostic instrument capable of ruling out carcinoma of the corpus, which is not a rare complication in a myomatous uterus At the same time curettage is a well known hemostatic measure It removes bleeding endometrium stimulates tonicity of the myometrium, and often regulates ovarian function Almost one third of menorrhagias due to benign causes are arrested permanently by thorough curettage in the young woman and the figure rises to almost two thirds for the menopausal and premenopausal group

Definitive Treatment

The ideal causal therapy for any tumor is removal of the new growth without alteration of function in the host organ and with smallest possible risk to the patient

Myomectomy is the method by which this ideal may be attained in the occasional patient For best results this procedure demands a pedunculated or superficially subserous myoma or myomas easily approached by laparotomy Since in most patients there are intramural tumors too great in number to be removed safely and/or too small in size to be seen recurrence of large or symptomatic myomas occurs too often to make myomectomy universally acceptable as definitive therapy For the same reason the procedure is best limited to patients under 40 years of age Menorrhagia will persist after myomectomy in a substantial propor

mors, deriving blood supply from foreign tissues

SYMPTOMS

Symptoms associated with myomas are bleeding pain, pressure phenomena in fertility and complications of pregnancy

Abnormal bleeding is most commonly in the form of hypermenorrhea (menorrhagia) as a consequence of associated hormonal disturbances and/or loss of contractility of the myometrium with insufficient compression of blood vessels

Metrorrhagia results from loss of surface continuity of the epithelial lining of the uterine cavity, from necrosis of a hyperplastic endometrium or from ulceration caused by pressure atrophy of the endometrium Carcinoma of the endometrium or cervix or pedunculation of a submucous myoma must also be considered

Myomas may also be accompanied by sterility or complications of pregnancy especially abortion premature labor, and abnormal presentations

Pressure symptoms on bladder or rectum may be caused by the weight of a large myoma in the abdominal cavity or by tumors in the lower half of the uterus

Pain may result from stretching or rupture of the capsule edema infection, rapid growth ischemic degeneration, axial rotation of the myomatous uterus, or torsion of a pedunculated tumor

DIAGNOSIS

Diagnosis of myomas of the uterus is *made most frequently by two procedures* Bimanual palpation helps to rule out adnexal masses, while diagnostic curettage may result in recognition of distortion of the uterine cavity by submucous growths and procures tissue for microscopic search for possible endometrial carcinoma Submucous fibroids may be discovered by roentgen uterosalpingography, while culdoscopy or pneumoperitoneum may serve to separate subserous tumors from adnexal enlargements without the necessity of recourse to exploratory laparotomy The latter must not be avoided if the total bulk of the pelvic masses is greater than that of a three months' gestation or if ovarian tumors can not be ruled out by other means Roentgen examination of the lower abdomen and pelvis for fetal skeleton may be indicated where a large myomatous mass cannot be differentiated from pregnancy Biologic tests for pregnancy also must be used in this instance Simultaneous occurrence of pregnancy and myoma should always be considered

TREATMENT

There are three general methods of treatment of myomas of the uterus These are (1) expectant treatment, or careful observation of the patient, (2) conservative, or symptomatic treatment usually curettage of the uterus to rule out malignancy and then treatment by certain hormones and other drugs (3) definitive, or causal treatment, which implies surgery or irradiation

Expectant Treatment

A myoma which is without symptoms and smaller than a 12 weeks old gestation requires no treatment Should a silent tumor be found by the physician, the patient should be informed only of the existence of some enlargement or thickening of the uterine muscle Anxiety must be prevented but the patient must be re evaluated at relatively frequent intervals at first to *determine the true size and the status of the* tumor in so far as growth is concerned If it becomes obvious that the tumor is benign and slow growing the interval between examinations may be lengthened

In the occasional patient with a silent myoma of the uterus sterility or habitual abortion may complicate the problem After all other possible causative factors have been eliminated with a relative de

available, irradiation is often further limited to the specific patient in this age group (40-50 years) who is a poor surgical risk

Irradiation therapy may be carried out by either roentgen ray castration technics or intrauterine radium insertion Roentgen therapy is given bilaterally through anterior and posterior skin portals over the ovarian regions Total dosage depends *upon the girth of the patient, about 500-700 r* should reach each ovary, the dose varying in inverse relationship to the age of the patient Obesity is a contraindication Intracavitary radium acts largely as a hemostatic upon the uterus itself, generally not resulting in complete castration This is of importance to younger women who have not entered the menopausal period in that psychologic trauma will be minimized by the absence of abruptly beginning severe 'hot flushes,' and other distressing symptoms

Adequate radium therapy requires a dosage of 1600-2400 milligram hours The number and potency of capsules inserted depends upon the size of the uterine cavity above the internal os Irradiation to the cervix and subsequent stenosis may be obviated by use of a 'dummy capsule in the cervical canal A cavity so large as to allow extreme mobility and leaning of the usual tandem of capsules is a contraindication to radium

When arranging for radiation therapy for a uterine myoma provision should be made also for certain associated measures There are four accessory steps necessary for *the safe handling* of the case They are (1) deep pelvic palpation under anesthesia to rule out ovarian enlargement and adnexal inflammatory changes, (2) thorough uterine curettage to discover early endometrial carcinoma and any pedunculated submucous tumors, (3) cervical conization when chronic cervicitis or other local lesions exist, and (4) meticulous recording of all data *from the examination, to better allow early* recognition of any ovarian enlargement at future follow up examinations of the patient If no grossly suspicious tissue is found by curettage or in the cervix, radium insertion may be done immediately

Check up examinations in the climacteric age should be carried out at least every six months

tion of cases, and may or may not then respond to symptomatic measures. Metrorrhagia from pedunculated submucous growths appearing in the vagina is readily relieved by excision and high ligation of the pedicle through the cervix, but anterior hysterotomy is needed to properly approach tumors with short pedicles.

Myomectomy is of great value where the integrity of a pregnancy has been threatened by severe reaction in a degenerating myoma and conservative therapy has been of no avail. Myomectomy involving any but definitely pedunculated tumors with relatively poor blood supply is contraindicated at cesarean section. If surgery is deemed necessary at this time or immediately following vaginal delivery, *total* hysterectomy is the procedure of choice.

When symptoms warrant active therapy, surgery in the form of exploratory laparotomy is indicated if a positive diagnosis of uterine myoma cannot be made and the differential diagnosis revolves about the degenerating fibroid, ovarian cystoma or tubo-ovarian inflammatory tumor. Bilateral ovarian carcinoma may confusedly be considered a part of a pre-existing slowly enlarging multinodular myoma and the chances for a cure may be lost in observational neglect.

Hysterectomy. Hysterectomy remains the ultimate in definitive treatment of leiomyomas. To some physicians, unfortunately, it has become the chosen treatment for any myoma at any age, contraindicated only in the patient who is an extremely poor risk.

Accepted positive indications for removal of the uterus do exist. Some of these include metrorrhagic tumors in women under 40 and in senility, pain-producing growths of any size, myomas whose total bulk exceeds the size of a 14–15 weeks' pregnancy, rapid increase in size of any myoma, infected, degenerated, and multiple pedunculated tumors in women of all ages and myomas associated with adenomyosis or symptomatic chronic pelvic inflammatory disease. If curettage for excessive or irregular bleeding in a myomatous uterus has been productive of endometrium from which the diagnosis of malignancy cannot be ruled out with certainty, hysterectomy is the treatment of necessity. Removal of a relatively small 'fibroid' uterus through the vagina is accepted therapy in the patient requiring plastic repair for cystocele and rectocele with some degree of prolapse.

Unless the case is complicated by the presence of dense and limiting adhesions at the level of the cervix, from endometriosis or chronic pelvic inflammatory disease, present-day proper management dictates that the operation be a total hysterectomy rather than the subtotal variety. Alteration of normal vaginal physiology and postoperative complications are no more common in the total operation done by a capable surgeon; this procedure rids the patient of the definite risk of carcinoma in the cervical stump as well as too frequent discomfort in and around this residual organ.

While there exists considerable dispute over this phase of management, we prefer to remove even normal ovaries in most patients near 40 years of age or older, as well as any diseased ovary in younger women.

Irradiation. It is obvious from the above criteria that the presently accepted place for irradiation measured in the treatment of the myomatous uterus is a limited one. Irradiation is seriously considered only where abnormal bleeding (preferably menorrhagia or hypermenorrhea) occurs in the menopausal and immediately premenopausal woman with an otherwise symptomless, myomatous uterus no larger in bulk than a 12 weeks' pregnancy and devoid of pedunculated tumors. Where good hospital facilities and a capable surgeon are readily

The Ear

IN treatment of ear disease, the practitioner will be concerned with some common clinical entities foreign bodies in the ear canals including wax dermatitis of the auricle external otitis otitis media and Ménière s syndrome There are five important symptoms of ear disease ear pain (otalgia) discharge (otorrhea) hearing loss dizziness (vertigo) and ear noises (tinnitus) any or all of which may figure prominently in the diagnosis and treatment of the diseases

EXTERNAL EAR DISEASES

As in the case of other organs the external ear is subject to congenital deformities and defects This applies also to the external auditory canal The external ear is subject to the same diseases as any other skin covered organ including erysipelas impetigo contagiosa eczema seborrhoeic dermatitis herpes zoster oticus tuberculosis syphilis and leprosy Benign and malignant neoplasms may originate from any of the component parts of the external ear The condition may be limited to the auricle itself but often extends from the scalp face or external auditory canal A skin affection of the ear co existing with some pathologic process in the canal is commonly observed Disease is occasionally transmitted to the skin of the ear by contact The influence of constitutional disorders and organic diseases must always be considered

Dermatitis of the auricle frequently co exists with an inflammatory dermatitis of the external auditory canal and must be treated in conjunction with the latter The skin of the auricle is exposed to the elements to irritants of all kinds trauma excoriations from scratching It responds by inflammation as does skin elsewhere in the body to irritating medications applied to it or coming in contact with it It may be sensitized by protein elements of cosmetics soaps or lotions applied to the facial area The auricle becomes tender, swollen red and in bacterial inflammation, hot When systemic evidence of fever, leukocytosis and chills are present, erysipelas of the auricle must be differentiated from the other conditions mentioned *

When eczema or a seborrhoeic dermatitis of the auricle occurs it may be present as part of a generalized epidermal reaction seen also on the face eyelids and flexor surfaces of the elbows and knees If the auricle alone is involved the posterior aspect in the intertriginous areas shows the typical crusting excoriation oozing and hypertrophic areas For eczemas limited to the auricle treatment consists of a search for the offending medication cosmetic or irritant and an attempt to remove the source The lesions themselves if acutely inflamed are treated by wet packs of Burow s solution 5 parts of crude alum and 25 parts of lead acetate, dissolved in 500 parts of water

If the external auditory canal is also involved it should be cleaned carefully and a gauze wick soaked in Burow s solution gently placed in the canal and kept moist by the addition of drops of the solution As the acute episode passes and the oozing redness and tenderness are alleviated soothing ointments may be used *

External Canal

Foreign bodies in the external canal may be of various types (1) animate such as insects etc (2) inanimate consisting of any small object (3) hygroscopic bodies which are liable to swell such as beans or wheat

* See Chapter 58

36. *Otolaryngologic Diseases*

FRANCIS L. LEDERER
& RICHARD E. MARCUS

DISEASES of the head and neck are treated best when they are properly diagnosed Fundamental to all diagnosis is a definitive history and a complete physical examination Head and neck disease is interpreted in relation to complete body function although it does have certain regional characteristics The practitioner with a knowledge of otolaryngologic symptomatology, together with an acquaintance with the technics employed in examination, and keenly aware of the whole man, is able to determine a rational course of action (medical or surgical) for his patient A course of action may include a proper antimicrobial agent, the local application of medication a biopsy or further diagnostic measures observation or reassurance A background knowledge of otolaryngologic symptomatology includes an acquaintance with the significance of head or neck pains nasal obstruction discharge, or bleeding burning sensations of the mouth and tongue, dysphagia cough, hoarseness, dyspnea tinnitus, otalgia, vertigo, and hearing loss A background knowledge of otolaryngologic examination implies a familiarity with the use of the head mirror, nasal speculum, tongue depressor, ability to perform nasopharyngeal inspection by indirect and direct means, mirror examination of the larynx, the proper placement of an ear speculum, hearing tests, sinus transillumination and an understanding of roentgenographic study of the head and neck areas In other words, the same course of action is essential to a successful otolaryngologic approach as it is to medicine in general There are no short cuts"

Basic knowledge of anatomy and physiology may be used to excellent advantage in the interpretation of the specific nature of any given case A color change, an alteration in contour, a modification of normal function, with or without specific complaints referable to the region stimulates association of what is observed with some pathologic state The physician should then proceed to utilize all adjuncts to diagnosis, including the clinical and roentgen ray laboratories

A good diagnostician is a good listener Although it takes a long time to obtain a complete history, nonetheless it is worth while A good doctor must listen with what has appropriately been referred to as the 'third ear', that is, with understanding, or empathy In addition, common sense must be accorded its rightful place in diagnosis and treatment

occasionally the visualization of a red, indurated process on the skin of the external canal in or about the vestibule Symptoms are very intense in proportion to the local findings With formation of a periauricular abscess the symptoms are more pronounced Pus is present, especially if the process is associated with otitis media suppurativa Edema around the ear and over the mastoid region even involving the eyelids on the affected side is seen in some patients The ear is often displaced forward Lymph adenopathy over the mastoid in the cervical region and in front of the tragus is usually present Hearing is not impaired unless the canal is occluded by the swelling In the average case a furuncle can be seen on otoscopic examination Pulling of the pinna or pressing on the tragus produces pain

The cardinal differential point in otitis media mastoiditis and furunculosis is the negligible reduction in hearing in furunculosis while in mastoiditis and otitis media the reduction is marked In furunculosis tenderness over the mastoid is elicited on superficial pressure lifting the auricle or pressing on the tragus, while in mastoiditis it is deeply seated The retroauricular groove is obliterated in otitis externa but not in mastoiditis

Treatment The ear-canal furuncle should be managed conservatively by the use of hot fomentations and analgesics Use of ear drops is not recommended Incision of the furuncle should not be done unless pointing can be visualized Occasionally contiguous hair follicles are involved in a spreading process resembling occipital carbuncles These should be treated by the use of one of the antibiotics specific for the gram positive cocci and by wide incision drainage and packing when pointing and softening occur The pack should be changed and shortened each day until healing occurs usually in about seven to ten days

Diffuse External Otitis

This condition is characterized by three stages acute, subacute, and chronic It is an inflammation of the epidermis involving all layers and extending throughout the external auditory canal It is most often seen in its acute phase during the summer months and seems to be closely related to swimming Apparently, the macerating effect of exposure to water reduces the local epidermal resistance to pathogenic bacteria in the water or the ear canal Within hours the patient complains of pain in the ear feels feverish, and notices that any pressure on the ear is extremely uncomfortable Shortly thereafter the pain becomes intense and medical help is sought The physician finds the auricle tender to motion elevation of temperature (which may go up to 102° or 103° F) and swelling of the skin of the canal so that the external auditory meatus may be slitlike as compared to the uninvolved side (although both may be involved in the process) The preauricular lymph node may be palpable and tender At this stage the treatment should consist of one of the antibiotics specific for the gram positive organisms hot fomentations to the ear, analgesics and possibly morphine (10 mg) hypodermically for the extreme pain The external auditory canal should not be manipulated ear drops should not be used Antibiotics should be continued for three to four days uninterruptedly in spite of what appears to be general improvement In about a week all evidence of the swelling and pain should disappear, and in many instances the disease process has been resolved The patient should be advised against swimming for the rest of the year in that area If an epidemic type of involvement occurs the swimming areas should be inspected for contamination and measures taken to eliminate the source of infection

In some instances the acute episode passes into a subacute phase, characterized by a thin greenish discharge which has a

and (4) cerumen (wax) in the canal (secretion anomaly) Animate foreign bodies in the ear are commonly found in inmates of large institutions who suffer from lack of personal hygiene Small objects of every possible kind have been removed from the auditory canal The diagnosis of a foreign body in the canal is based on the history, symptomatology, and examination of the canal

Cerumen Some form of wax collection occurs in the ear canals of most people, and is due to excessive secretion of the ceruminous glands The wax may be soft and oily, or become desiccated and firmly implanted in the canal There is usually no difficulty noticed by the patient unless the lodgement becomes of such size as to interfere with normal hearing or unless the patient or others make attempts to remove the plug irritating the delicate skin of the canal and causing inflammation of the skin Sometimes the patient will complain of ringing in the ear or a sense of fulness, perhaps even pain, if the wax plug becomes pushed near the tympanic membrane

The ear canal should be carefully inspected and the physician should inquire as to whether or not the patient has a perforated ear drum or has had previous middle ear disease Approximately 1 out of 10 patients who have occluding wax have ear drum changes including atrophic scars and perforations If removal can be attained by using a rounded wire ear loop (not a sharp curette) and careful manipulation under reflected light, it is preferred to syringing At least, in this manner enough of the wax can be removed to have a clear view of the tympanic membrane If the drum membrane is intact, the rest of the wax may be removed by syringing with a 200-cc metal syringe The stream of water should be directed along the upper, posterior wall of the canal It may be necessary to soften very hard wax by instilling the following solution into the ear twice daily

	Gm or cc
Sodium bicarbonate	0 78
Glycerin	3 75
Water to make	15 0

The patient should return in a day or two and have the tympanic membrane inspected and hearing acuity assessed after removal of wax

Foreign Bodies Beans, seeds and hygroscopic objects should be removed by syringing with 95 per cent alcohol to prevent swelling of the impacted body The stream must be directed against the canal wall and not toward the foreign body, as it may be pushed past the bony isthmus toward the ear drum, making removal difficult *For the removal of other objects and* after the type of foreign body has been ascertained by examination, the following should be tried

1 Syringing with warm water at 105° F, *oil, or alcohol The character of the foreign* body determines which of these should be employed for irrigating purposes

2 Mechanical removal by means of forceps ear spoons, or hooked instruments This should be attempted only by one who is skilled and thoroughly familiar with the anatomy of the external canal In children, general anesthesia is essential for absolute control of the patient

3 Postauricular incision is *seldom* indicated Objects which are so firm that they cannot be broken and are pushed beyond the isthmus or into the middle ear, will occasionally require posterior approach

Furunculosis

Furunculosis, which is a circumscribed type of external otitis is caused by infection of the hair follicles and sebaceous glands *of the membranous portion of the external* canal This condition is diagnosed by the point of tenderness (found by finger or cotton tipped applicator palpation of the area), pain on motion of the auricle, and

TABLE 51 DIFFERENTIAL DIAGNOSIS OF ACUTE OTITIS MEDIA AND ACUTE DIFFUSE EXTERNAL OTITIS

	Acute otitis media	*Acute diffuse external otitis*
Onset	Sudden, but usually in association with or after an upper respiratory infection in winter months	Sudden but usually unrelated to upper respiratory infection, occurring in hot summer months most often after swimming
Pain	Severe, deep, boring, unrelated to movement or pressure on auricle	Moderate to severe, more tactile, and accentuated by movement or pressure on auricle
Fever	High in young children, with gastrointestinal symptoms, variable in adults	Slight to moderate in all ages
Discharge	None, if tympanic membrane perforation has not occurred, profuse mucopurulent discharge after perforation	Usually a slight, thin, greenish exudate rather than discharge
Preauricular tenderness (preauricular node)	Rarely present	Rarely absent
Hearing	Moderately to markedly diminished should be tested by masking good ear	No diminution or slight loss of hearing
Tuning fork tests	Weber test lateralizes to involved side, Rinne test is negative	Weber test occasionally lateralizes to involved side Rinne test is positive
Otoscopic picture	Reddened or beefy drum, perhaps bulging distorted or absent light reflex	Unable to see drum because of marked edema of canal if seen, drum has usual pearl gray translucency

fluid in the middle ear cavity The treatment is paracentesis followed by eustachian tube catheterization once or twice to evacuate the serous or mucoserous exudate After the first stages the tympanic membrane shows a diffuse or localized thickening or atrophy and calcareous deposits It is dull and lusterless, with a retraction that is marked and permanent

Acute Otitis Media

Following a severe head cold, acute otitis media is ushered in by pain in the ear which is persistent and severe, often *throbbing sticking*, and radiating Relief is usually afforded the moment perforation of the drum takes place The pain may be referred to a tooth or to the eye In adults, the temperature for several days varies from 100° to 102° F, but in children it may reach 105° F When the temperature is high, the symptoms simulate meningitis In very young children, chills and even convulsions are not uncommon Tinnitus of a roaring, pulsating character is usually present Dizziness with nystagmus is a serious sign, especially if the patient complains that objects turn around him (labyrinthitis) Tenderness over the mastoid, due to periostitis (mastoidism) is elicited even before the drum ruptures and persists for some days after the discharge becomes established If a pulsatory discharge through a perforation persists after two or three weeks it indicates considerable hyperemia in the tympanum

This type of otitis normally undergoes three stages The transition from one to another often involves very little time in some instances only a few hours The first stage is the period of inflammation and pain the second a stage of secretion, and the third a period of resolution and cessation of suppuration Acute middle ear disease (1) must be differentiated from the acute diffuse external otitis just described,

tendency to excoriate the skin of the vestibule and auricle occasionally involving the auricle in an acute inflammatory eczema The inflammation of the auricle should be treated in conjunction with the treatment of the external otitis of the canal The canal if it is not tender must be carefully cleansed under direct vision using the cotton tipped applicator or a normal saline wash with the ear syringe Burow s solution 0 5 per cent on a gauze wick should be inserted gently into the canal six to eight times per day for twenty four to forty eight hours and then discontinued The canal should be inspected again carefully and if satisfactory progress has been made the natural healing process should not be disturbed by other medication If after a week to ten days of treatment and observation (in the subacute phase) no final healing has taken place the physician should consider using one of the keratolytic agents in the ear

	Gm or cc
Chrysarobin	0 3
Salicylic acid	0 6
Emulsion base to make	30 0

Label Apply locally to ears as directed

In spite of all efforts the external diffuse otitis may become a chronic disease with remissions and acute exacerbations all medications being unavailing and in some instances harmful The patient must avoid getting water in the ears and all manipulation of the vestibule and the canal by the fingers must be discouraged The treatment should be symptomatic for the exacerbations Radiation therapy is not indicated

MIDDLE EAR DISEASE

The tympanic membrane may suffer effects from local or remote injuries The former embraces a wide variety of factors the latter may include severe accidents such as basal skull *fracture* *Myringitis bullosa* is a condition in which blebs or bullae form on the drum or external canal It is thought to be of viral origin being similar to herpes Calcareous deposits on the tympanic membrane are not especially significant from a pathologic viewpoint although they occasionally interfere with the hearing function and usually represent previous middle ear inflammation or even the healing of a perforated tympanic membrane

The tympanic cavity is affected either directly by way of the drum membrane or indirectly through the eustachian tube The latter route is the more common of the two In this connection the influence of head colds and upper respiratory infection should be considered The nose nasopharynx and accessory sinuses are common sources of infection which by anatomic contiguity involve the eustachian tube Pain is occasionally associated with blockage of the eustachian tube Characteristically however there is a dull heavy feeling in the head on the affected side Tinnitus is usually present even persisting after all other symptoms have subsided and is often the only symptom which compels the patient to seek medical advice The degree of deafness is subject to great variation The patient describes a sensation of talking to himself (autophony) or listening to a sea shell Children especially when both ears become involved become inattentive and listless (aprosexia) Various aural phenomena may occur such as hyperesthesia acoustica (especially for high notes) or dysacousia (voices become distorted and cause discomfort hearing tones too high or too low)

Otalgia in or about the ear may be due to causes other than otitic. This is significant especially in the presence of a normal appearing tympanic membrane There are many patients whose only complaint is some fullness in one or both ears and a hearing loss There is no pain although there may be *transitory aural vertigo* and nausea Examination of the ear drum reveals a chalky white malleus and a collection of

perforation is treated by local nasopharyngeal and nasal measures powders or alcohol drops in the ear and perhaps the use of specific antibiotics It must be differentiated from the more critical marginal perforations by evaluation of the tympanic membrane picture hearing function roentgen rays and labyrinthine studies

INTERNAL EAR

Vertigo

Vertigo is the most prominent complaint identified with disturbances of the internal ear There is considerable confusion not only in the nomenclature but also in the definition of vertigo It is important to determine whether the vertigo is of a labyrinthine or nonlabyrinthine character and especially in the former case whether it is of a central or peripheral origin Vertigo does not constitute an objective symptom Differential diagnosis based upon clinical experience must remain tentative Labyrinthine vertigo usually will be rotational directional or systematic while nonlabyrinthine vertigo is nonrotational nondirectional and asystematic The latter comprises various sensations of dizziness such as found in diseases of the cardiovascular system gastrointestinal disturbances endocrine dysfunction and visual disturbances

Peripheral labyrinthine vertigo occurs in paroxysms lasting for approximately one minute The vertigo may occur when the head is suddenly turned or moved Consciousness is not lost and a spontaneous nystagmus is always present during an attack The course of peripheral vertigo is self limited whereas vertigo of central origin is usually progressive and lasts over a long period of time Otoscopic findings are often positive in the peripheral type and usually negative in the central type the reverse is true for neurologic findings

Treatment The application of antihistaminic drugs in motion sickness started their wide use with satisfactory results in the medical management of non specific vertigo due to trauma as well as in a large percentage of cases of Ménière s disease It has been long recognized that a hydrops or effusion of the labyrinth is a basic pathologic change in some of these cases and sensitivity to histamine has been postulated as a cause Favorable responses have followed the use of antihistaminic drugs administered in dosage comparable to those recommended for motion sickness However these responses are not universal Interest in vertigo has resulted in refined technics for the diagnosis of hydrops of the labyrinth and in the surgical therapy of cases which do not respond to drugs Formerly Dandy s operation with dissection of the eighth nerve represented a difficult and extensive surgical procedure It is now possible by a relatively simple operation involving an endaural approach to bring about a selective destruction of the inner ear This consists of destroying the membranous labyrinth and preserving the normal anatomic relationships and function of the cochlea After carrying out a modified radical mastoid operation the horizontal semicircular canal is exposed and a bony fistula similar to that made in a fenestration operation is created through which the membranous labyrinth is coagulated with an electric current in order to obliterate the vestibule Other technics of obliteration by means of bone dust or cartilage introduced into the fistula have also been suggested The results are histologically proved in animals patients lose their vertigo and retain good hearing

The Hard of Hearing Patient

In World War II 4 out of every 1000 rejections for military service among the 18 to 19 year olds was because of hearing deficiencies or ear disease In combat hearing defects occurred as a result of heavy fire and

(2) medical treatment must be understood in terms of its limitations and (3) complications must be discovered early

Differentiation from acute diffuse external otitis is sometimes difficult even in experienced hands Table 51 may be of some value

Treatment The treatment of acute otitis media includes the use of antibiotics and paracentesis when indicated Many of the acute episodes do not become purulent and will resolve without medication of any kind When a diagnosis of inflammatory otitis media is made the antibiotics and/or paracentesis may be withheld if the physician can note changes almost hourly in the membrane and middle ear cavity The acute otitis media that requires penicillin also requires paracentesis For many patients who cannot be followed as carefully antibiotics can be used 0 25 Gm chloramphenicol after food every three hours for four doses then every six hours for four days or 600 000 units of penicillin with aluminum monostearate intramuscularly daily for four to five days Analgesics are to be used morphine if necessary Ear drops should not be used as they are too frequently depended upon for analgesia to the neglect of evaluation of the drum changes after the pain subsides Acute otitis media with suppuration needs paracentesis intracranial complications such as mastoiditis septicemia and labyrinthitis still occur even in adequately treated or fulminant cases Hearing should be tested after every episode of otitis media by all clinical means including pure tone audiometry

In every case of otitis accompanied by fever the other ear should be examined repeatedly and the early signs of complications such as central pneumonia acute surgical mastoiditis petrositis extradural abscess sinus thrombosis endocarditis pyemic metastases labyrinthitis and cerebral abscess must be recognized

Chronic Otitis Media

Chronic otitis media may follow an acute suppurative process Differentiation from the less harmful suppuration of the mucous membrane of the middle ear (mesotympanic defect of the tympanic membrane) in the lower or middle parts of the drum is made by the lack of pain or marked middle ear deafness Offering more of a threat to life is an attic suppuration in which there is headache reduction in hearing (inner ear) and a fetid discharge which persists despite local treatment Subjective symptoms are usually entirely absent in chronic suppurative otitis media but over 90 per cent of the chronic suppurations with epitympanic perforations are complicated by cholesteatoma These cases are always a source of concern because of potential intracranial complications

The chronically discharging ear must be investigated carefully by means of a good history and otoscopic examination A differentiation must be made between chronic suppurative otitis media and chronic diffuse external otitis The hearing loss Weber lateralization to involved side negative Rinne on that side and perforation of the ear drum are the four qualifications for a diagnosis of chronic suppurative otitis media

All chronic suppurations of the middle ear are potentially dangerous The most common cause of brain abscess meningitis and labyrinthitis is the chronic middle ear suppuration with a posterior superior marginal drum perforation or Shrapnell s membrane changes with cholesteatoma The treatment of the chronic suppuration with marginal perforations and temporal bone erosions as determined by roentgen ray is a surgical mastoidectomy The final decision as to when to operate and the type of mastoidectomy to perform can be made only after careful evaluation of the individual case Chronic middle ear suppuration with a central tympanic membrane

Nose and Sinuses

RHINITIS

The *common cold* is a contagious disease and is the forerunner of a large number of serious or even fatal ailments One of the first manifestations of a cold is acute rhinitis

Simple chronic rhinitis is attributed to prolonged irritation from nasal obstruction latent sinusitis and recurrent attacks of acute rhinitis

Hypertrophic rhinitis is a chronic inflammatory process which involves the inferior turbinates producing obstructive symptoms and increased secretion When the hyperplastic stage of inflammation of the nasal membranes is followed by atrophic changes sometimes also involving the underlying bony structure the affection is known as *atrophic rhinitis* In this condition the nasal chambers become widely dilated and the accumulated secretions undergo decomposition with crust formation and foul odor

Vasomotor rhinitis is a condition characterized by intermittent engorgement of the nasal mucosa sneezing associated with a free flow of diluted mucus and nasal obstruction The disease is perennial in its course and commonly caused by allergic factors Hay fever is seasonal and is always a true allergic affection

Hyperplasic rhinitis denotes tissue changes due to long continued attacks of chronic rhinitis or sinusitis

The nasal neuroses include anosmia hyperosmia hyposmia parosmia spasmodic sneezing and reflex nasal neuroses The mechanism of each of these states is different and gives rise to peculiar symptoms

Purulent rhinitis is an inflammation of the nasal mucous membrane in which the discharge is purulent from the beginning of the condition Young undernourished children are most commonly afflicted The infection is due to specific causes such as exanthematous disease Purulent rhinitis is occasionally associated with purulent nasopharyngitis Foreign bodies suppuration of the accessory sinus cavities and tuberculous or syphilitic disease should be excluded as a cause of the purulent discharge by a thorough examination of the anterior nasal cavities

The *nasal septum* is a partition which separates the nasal cavities It may be congenitally absent deviated subluxated or have numerous projections such as spurs and ridges ecchondroses and exostoses it may be subject to the formation of hematomas and abscesses may contain perforations caused by trauma or disease or may become adherent to the neighboring wall as the result of adhesive bands (synechia) Many neoplasms also involve the nasal septum Atresia or imperforation of the choanae or of the pharynx is partial or complete unilateral or bilateral and is congenital or acquired

The nose may be the site of numerous psychogenic and neurologic reflexes inflammatory states and neoplastic conditions all of which may lead to local or referred pain It is well to remember that since patients may suffer from marked sinusitis and yet not suffer from head pain the reverse may also be true The severity of the pain is not always in proportion to the degree of involvement of the sinus or sinuses

THE PARANASAL SINUSES

There are four pairs of paranasal sinuses the maxillary ethmoid frontal and sphenoid In spite of lack of specific knowledge of sinus function it is apparent that these relatively large air spaces are prone to various diseases the most common being

in some cases were superimposed upon pre existing ear disease

In recent years, special emphasis has been placed upon the field of audiology as a basic science related to medicine There is great concern for the millions of hearing and speech handicapped children and adults for whom the physician must provide clinical service including effective and orderly rehabilitation As the speech and *hearing handicapped child is criticized by* his family or taunted by his playmates, so the adult is at a disadvantage in social communication Conversations with him become struggles accentuated by frequent interruptions and embarrassment He loses self confidence in social situations and becomes aggressive or withdraws entirely, frequently he comes to regard himself as peculiar or eccentric and moves steadily into the attitude of self pity and antisociality He worries about his job or may be discharged for insubordination or noncompliance as a result of his hostility

In the young child local ear disease must be differentiated from aphasia mental retardation and psychiatric and emotional disabilities many of which masquerade as cochlear disease The greatest patience must be exercised by the physician in the examination of the so-called uncooperative child Encouraging parents to seek aid early in ear disease is of prime necessity Proper treatment of low-grade ear infections as well as recognition of their effect upon hearing and of the dangerous character of the chronic discharging ear, require emphasis When applied early, remedial measures medical as well as surgical may still be effective before irreparable damage is done

When the physician after careful evaluation believes that he is dealing with permanent hearing loss he should turn to rehabilitative procedures These are designed to make full use of the patient's residual hearing by education and retraining using amplification when possible Vocational readjustment, psychosocial readaptation, redirection of energies, and physical reconditioning are desirable goals in the utilization of residual hearing Rehabilitation centers have been established in many cities to provide thorough medical *and otologic examinations, audiometric,* auricular, and other functional tests of hearing The fitting of hearing aids, auditory training instruction in speech reading —all may be carried out under the guidance of the otologist The value of an aid is increased by training in the technic of its use Special training may improve comprehension of words and sentences Lip-reading is especially practical when combined with a hearing device In a few cases of otosclerosis, the fenestration operation may restore hearing to a practical level However, the results of this operation, even when performed by the most skilled and experienced surgeon and in the most ideally suited case, are still somewhat uncertain, since there is at least one chance in five that the patient will be disappointed in the result

The physician should know more about the causes of hearing loss in the newborn and the effect of extra and intrauterine influences on the development of the otic capsule Attention already has been focused upon the profound effect of maternal rubella in the development of congenital *deafness In addition, there has been* a recent effort to emphasize the changes in hearing associated with Rh incompatibilities Further integration in research with workers in electronics physiology, acoustics, and education is a necessity

be made on the following points (1) history of upper respiratory infection headache and malaise (2) possible swelling about the eyelids (3) pus in the nose bilaterally or unilaterally and (4) clear transillumination of frontals and antra If the diagnosis is not clear roentgenographs of the sinuses will help to define the location and extent of ethmoid sphenoid or other sinus involvement

Treatment The modern treatment of acute sinusitis to a great extent involves the use of the proper antibiotics Since most cases of acute sinusitis are either of streptococcal or staphylococcal origin 300 000 units of penicillin intramuscularly daily for five to seven days with other supportive measures is very effective These supportive measures include

- Bed rest for the first three to four days
- Anodynes preferably acetylsalicylic acid 0 3 Gm every hour for three hours if necessary Occasionally codeine 30 mg or morphine sulfate 15 mg may be necessary to relieve the pain
- Hot wet towels to forehead and/or face for twenty minutes every hour while awake for the first day or two Exposure to infrared lamp for the same time but at a conservative distance may be prescribed
- Use of a bland nasal constrictor in a home atomizer or by drop prior to the application of the hot towel Ephedrine sulfate (0 5 per cent) in isotonic saline solution *or neosynephrine hydrochloride (0 25* per cent) in isotonic saline solution can be used during the acute phase for children or adults Nasal constrictors should not be used for more than a week at a time The prolonged or promiscuous use of nasal constrictors is to be condemned since nasal hypertrophy and atrophy may result
- Gentle nasal suction in the supine position after the acute phase has passed daily or three times weekly until the suppuration has stopped

Chronic Sinusitis

Acute sinusitis may become a chronic inflammation with continuous nasal suppuration and sporadic headache In these instances there may be evidence of obstruction of the sinus ostia by marked septal deviation anomalous enlargements of one or more of the turbinates hyperplasia or polyposis of the nasal mucosa due to allergy or to the chronicity of the infection or some previously overlooked intrasinal lesion A tortuous nasofrontal duct or anomalous sinus cells may prolong or propagate infection Here the local nasal condition must be corrected by surgical manipulation if necessary and careful nasal suction should be performed in the supine head low position three times weekly preceded by shrinkage of the nasal mucosa The use of the antibiotics is not too satisfactory In any acute subacute or chronic sinusitis the usual criteria for the selection of antibiotics is used depending on the type of bacteria found on culture and its susceptibility to the particular antibiotic agent under consideration *

Complications Complications of sinusitis vary from some simple local manifestations to severe brain or systemic conditions They are grouped as

- I Pharyngitis tonsillitis and laryngitis
- II Auricular
- III Bronchopulmonary
  - A Bronchitis
  - B Asthma
  - C Bronchiectasis
  - D Lung abscess
- IV Ocular
  - A Optic neuritis
  - B Orbital cellulitis and abscess
- V Endocranial
  - A Meningitis
  - B Brain abscess
  - C Cavernous sinus thrombosis
- VI Renal
- VII Gastrointestinal
- VIII Systemic

* See Chapter 4

inflammations and allergies or a combination of the two Because of their location in the skull any lesion of the sinuses can cause head pain local, contiguous, or referred The usual cause of sinus inflammation is the head cold with subsequent suppuration in one or more of the sinuses The respiratory epithelium shows inflammatory response with marked blood vessel engorgement increase in numbers of goblet cells local epithelial destruction and exudation

Acute Sinusitis

The clinical pattern of acute sinusitis usually appears a week to ten days after the onset of the upper respiratory infection There is a latent period of a few days to a week or ten days when it seems the rhinitis is subsiding The patient then suffers headache the location of which depends on the sinus involved increased nasal suppuration (unilateral or bilateral) malaise, and some elevation of temperature Although there are typical headaches depending on the involved sinus it is well not to be restricted to the textbook picture but rather to consider an investigation of all the sinuses Involvement of the maxillary sinuses usually causes pain in the cheek or upper teeth in addition to severe aching in the forehead or behind the eye However headache may be located almost anywhere in the upper face and head in any sinus infection

In addition to the history of recent head cold or of nasal allergy perennial or seasonal the diagnosis of sinus disease can be made by physical findings Gentle finger tip percussion or pressure in a line over the orbital ridge may disclose tenderness over one or both frontal sinuses The same procedure over the malar bone prominences and soft tissues of the cheeks may elicit a similar tenderness as a result of underlying maxillary sinus inflammation By placing the tip of the small finger along the soft tissue of the inner canthus of the eye and pressing gently inwardly and medially, ethmoid sinus tenderness may be found If pressed upward in the same location, frontal sinus involvement may be detected

Transillumination of the sinuses, by means of a special attachment to the ophthalmoscopic battery case, is a necessity in routine office examination of the sinuses The procedure is carried out in a completely dark room The tip of the transilluminator is placed gently in the soft tissue of the upper eyelid just above and lateral to the inner canthus Uninvolved frontal sinuses will be revealed by the red glow of the transmitted light through the clear air space The absence of the red glow for one or both frontal sinuses may mean either a restricted or absent pneumatization which is a relatively common anomaly The frontal sinuses do not reach full development until shortly before or during adolescence From 3 to 4 per cent of the population have undeveloped frontal sinuses on one or both sides Other clinical findings will substantiate the diagnosis of frontal sinusitis

The maxillary sinuses are transilluminated by placing the tip of the light into the soft tissue of the lower lid above the infraorbital margin below and lateral to the inner canthus The patient's mouth must be open and partial dentures and plates removed The examiner, holding the light tip steady in its position in the orbit, looks at the roof of the mouth from below Uninvolved maxillary sinuses will reflect the light through the relatively thin bone of the hard palate Failure to transmit light through one or both maxillaries indicates a space-filling lesion—inflammation with its accompanying suppuration, markedly thickened allergic or polypoid membrane or neoplastic epithelial or bone change

Neither the condition of the ethmoids nor the sphenoids can be visualized with certainty by office transillumination The diagnosis of ethmoiditis or sphenoiditis can

D Floor of nose
a Nasoalveolar cysts
b Labial cysts
III Nasopharyngeal
a Adenoids
b *Choanal* polyp
c Fibroma
d Malignant
IV Nasal sinusitis

Nasal polyps will become small, sometimes disappear, if allergic rhinitis is controlled When they show no sign of receding perhaps even becoming larger, they may be removed surgically by the snare under local anesthesia Microscopic study for possible malignancy should be done in every case If the ethmoid sinuses are involved in a chronic refractory purulence in association with severe, nonreceding polyposis a concomitant intranasal ethmoidectomy may be indicated This procedure should be employed as a last measure in carefully selected cases Results in such instances are good Promiscuous intranasal surgery should be discouraged, but on the other hand great harm can also be done by discouraging *all* nasal surgery

The use of a radium applicator should be withheld in almost all instances except after careful evaluation of symptoms and then only for children who have had previous adenoidectomy and antiallergic therapy

When severe nasal *septal deviations* can be proved as the primary cause of nasal obstruction the treatment is surgical, the classical submucous resection being the operation of choice Occasionally, septal plastic or associated nasal plastic procedures may be carried out Here again, the surgery must not be advocated without careful indication It is true however, that patients occasionally do have nasal obstruction due to septal deformities and good surgery will restore the nasal airway which is of such importance for comfort and sense of well being

The treatment for nasal obstruction caused by *foreign body* in the nasal airway one or both sides is removal This occasionally may become a major surgical procedure Foreign bodies in the nose occur frequently in children, less often in adults External force occasionally introduces some foreign body into the nasal cavity through its *roof, floor, or walls*

Inanimate foreign bodies are frequently introduced into the nose by young children and emotionally disturbed persons Every imaginable type of object has been removed from the nares They may result from external violence caused by gunshot and explosions Foreign bodies also enter the nasal cavity by way of the nasopharynx during vomiting sudden sneezing coughing, or during the act of swallowing Animate bodies such as insects, maggots and screw worms have been encountered in the nasal passages

The predominant symptoms are unilateral nasal obstruction pain epistaxis sneezing and a serous or purulent discharge The affected side is usually more prominent than the other, especially when such hygroscopic substances as peas or beans are present Abscess formation and necrosis of the cartilages and bones may occur Severe toxemias have occasionally followed

The history often leads to the diagnosis The presence of a foreign body is established by examination of the nasal cavities Polyps exostoses and sinusitis must be considered in the differential diagnosis When no history of a foreign body is obtainable examination of the anterior nares and palpation with the aid of a probe after the secretion is aspirated by suction will establish the diagnosis Roentgenograms promptly reveal opaque foreign bodies

The nature of the foreign body and the length of time it was retained will govern the method of therapeutic approach While removal is obviously the only rational treat

Treatment In the treatment of chronic *sinus disease the following program is rec* ommended

I Investigation of causes of chronicity
  A Systemic factors embodying allergic states endocrine and diet imbalance, general hygiene, and constitutional diseases
  B Local mechanical factors, such as a deviated septum polyps, intumescent and hypertrophied turbinates
  C Sinus infection per se in regard to mucosa bone, and dental involvements There is also the likelihood of *restitutio ad integrum* The relation of the infection to improper treatment, overtreatment and as a focus in arthritis nephritis headaches, *toxemia, mental depression* bronchitis, bronchiectasis lung abscess asthma, and gastrointestinal disorders is of importance

II Treatment is determined by the pathologic process in relation to the symptoms and present or potential effects In general, the correction of etiologic factors is important, and the most conservative *methods that have proved adequate suffice* These consist of nasal packs suction or sinus irrigation Submucous resection removal of polyps middle turbinectomy or infraction of the turbinate are the nasal operative procedures The maxillary sinus may be approached by a window beneath the inferior turbinate in the lateral nasal wall or by the sublabial route with removal *of the lining membrane of the sinus* The frontal, ethmoid, and sphenoid sinuses may be approached intranasally or externally The operation to be performed depends upon the sinus or sinuses affected the etiology of the disease its chronicity tendency, and course the age, socioeconomic status, and physical condition of the patient

Headache of nasal sinus origin may be caused by neoplasms, foreign bodies or retained dental roots Further diagnostic studies, including 'lipiodol' roentgen ray visualization, biopsy, or exploratory surgery *are often necessary* In the very refractory types of sinusitis, special cannulizations may be necessary for diagnosis as well as for treatment

NASAL OBSTRUCTION

Difficulty in breathing through the nose frequently leads the patient to consult a physician In itself, nasal blockage may constitute but a symptom of hypo or hyper function of the nose and does not make for a diagnosis The following outline indicates the causes of nasal obstruction

I Extranasal
  A Congenital defects
    1 Narrow bony bridge
    2 Atresia of the nares
    3 Thick columella
    4 Collapsed alae
    5 Depressed nasal tip
  B Acquired defects
    1 Depressed fractures
    2 Displaced cartilages
    3 Atresia of nares
    4 Neoplasms

II Intranasal
  A Congenital defects
    1 Nasal septum
    2 Lateral nasal walls
    3 Posterior choanae (atresia)
  B Acquired defects
    1 Nasal septum
      a Deviation
      b Hematoma
      c Abscess
    2 Infections
      a Acute
      b Chronic
      c Specific
    3 Foreign bodies
  C Lateral nasal wall
    1 Hyperplastic rhinitis
    2 Atrophic rhinitis (crusts)
    3 Allergic rhinitis
    4 Vasomotor rhinitis
    5 Neoplasms
      a Benign
      b Malignant

D Floor of nose
  a Nasoalveolar cysts
  b Labial cysts

III Nasopharyngeal
  a Adenoids
  b Choanal polyp
  c Fibroma
  d Malignant

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Animate foreign bodies or larvae of certain flies or parasites should be killed by the instillation into the nose of a weak solution of chloroform Removal is then performed with suction irrigation curettage or forceps

Rhinoliths usually contain an inorganic foreign body as a nucleus around which salts are deposited The symptoms are practically the same as those mentioned under inanimate foreign bodies As a rule they can be removed readily with forceps but the larger ones may have to be crushed first with strong forceps and then removed piecemeal

Nasal obstruction due to *tumors* in the nasopharynx other than lymphoid hyperplasia should be treated according to the particular neoplasm found This group includes growths situated on the posterior pharyngeal wall the roof of the nasopharynx or the lateral walls in the region of the tubal orifices These tumors occur at any time in life the early symptoms being nasal blockage a feeling of continuous head colds or the presence of a foreign body, blood tinged secretion or repeated hemorrhages cough disturbance of speech (rhinolalia clausa) and hearing headaches (neuralgic ocular systemic and metastatic groups) Many neurologic symptoms and symptom complexes occur such as unilateral amaurosis ophthalmoplegia trigeminal neuralgia involvement of the glossopharyngeal vagus and accessory nerves (jugular foramen syndrome) Pressure of a large mass on the tubal orifice and soft palate results in impaired hearing trigeminal neuralgia (second division) and asymmetry of the two arches of the palate (Trotter s triad) Such tumors have also been known to penetrate the orbit resulting in unilateral exophthalmus They involve the parotid and submaxillary region secondarily Squamous cell carcinoma is the most frequent malignant tumor, and appears as a slow growing firm movable sessile mass usually on the palate or lateral pharyngeal wall In the differential diagnosis of malignant tumors of the pharynx, syphilis tuberculosis and nasal fibromas must be considered

EPISTAXIS

The anterior part of the cartilaginous septum is usually the site of epistaxis—the locus Kiesselbach or Little s area This plexus of vessels is formed by the septal arteries and the terminal branches of the sphenopalatine artery

Nosebleed is primary or secondary spontaneous or induced and the cause is not always easily established Local causes of epistaxis are (1) Trauma such as nose picking (epistaxis digitorum) foreign bodies instrumental operative or from a blow on the nose (2) Ulcers due to trauma atrophic rhinitis membranous rhinitis tuberculosis syphilis and foreign bodies (3) Violent blowing or sneezing (4) Inhalation of irritating particles or gases (5) Hereditary angiomatosis and tumors both benign and malignant General or constitutional causes include (1) Blood disturbances as leukemia severe anemias purpura hemorrhagica and hemophilia (2) Blood vessel disease such as hypertension arteriosclerosis (3) High altitudes (4) The beginning of acute infectious fevers such as rheumatic fever diphtheria typhoid influenza or malaria and (5) Cardiac conditions

The nature of the pathologic process depends upon the causative factor, which in the majority of cases is an erosion of a superficial blood vessel Certain parts of the nose are not only more vascular than others but more exposed to traumatic factors These areas are usually on the anterior cartilaginous septum and the anterior end of the inferior or middle turbinate An

abrasion of a vessel will present nothing more than a bleeding point but inflammatory reactions or repeated nosebleeds will modify the character of the lesion

A heredofamilial angiomatosis with recurring epistaxis is occasionally designated as Rendu Osler Weber's disease It is a definite clinical entity a hemorrhagic dysplasia transmitted by and affecting both sexes but not sex bound This condition is characterized by repeated attacks of epistaxis telangiectasis of the skin and mucous membranes (lips tongue and septum) and the familial incidence of the disease The blood is usually morphologically and chemically normal except for the secondary anemia following hemorrhages

The *prognosis is good* if the epistaxis is due to some slight local lesion which can be eradicated or eliminated by proper nasal hygiene Death from ordinary forms of epistaxis is rare except in the angiomatous type which has an over all mortality of about 4 per cent

Treatment

Effective treatment of epistaxis calls for a determination of the cause of the bleeding The patient is usually more comfortable with his head erect since otherwise the blood trickles into the pharynx The patient can be instructed to place a pledget of cotton saturated with hydrogen peroxide into the bleeding side of his nose

A simple and frequently effective procedure after removal of the clot and temporary stoppage of the bleeding is to cauterize the affected area with a chromic acid bead or trichloracetic acid The dilated vessels and bleeding point can also be obliterated by superficial scarifications with a galvano cautery point Marked septal deviation should be corrected by submucous resection the mucosal flaps of the septum adhere together and obliterate the blood vessels responsible for the hemorrhage

In cases of the epistaxis caused by *arteriosclerosis or hypertension,* the flow may continue despite all efforts until the tension has been reduced In such cases an anterior pack or a postnasal plug or both must be used If severe arterial bleeding recurs after each removal of the tampon the external carotid artery or the internal maxillary artery should be ligated In instances of persistent bleeding especially after removal of polyps biopsy is indicated to exclude malignant growths

Often when chemical cauterization fails galvanocauterization or electrodesiccation promptly sears the superficial vessels with more or less permanent cessation of bleeding Preliminary analgesia by means of pontocaine or cocaine is essential

Throat

SORE THROAT

The patient who states that his throat is sore may mean that he has difficulty in swallowing or that he actually has pain somewhere in the nasopharynx pharynx posterior lingual area larynx or trachea Diagnosis cannot be based alone on pain or discomfort in any of these areas however specific symptoms in the oro and naso pharynx call for differential diagnosis and treatment If the tonsils alone are diseased the term tonsillitis is appropriate Involvement of all the pharyngeal structures requires designation by a more inclusive term as sore throat Angina has been defined as acute baneful or morbid inflammation of the entire pharynx and Waldeyer's lymphatic ring resulting from

ment, it is not always easily accomplished when the foreign body is embedded in the tissues and there is a marked inflammatory reaction

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TONSILLITIS

Acute infection of the tonsils is recognized by the sudden onset of hyperpyrexia chills or chilly sensations body aches dysphagia tenderness and enlargement of the cervical lymph nodes (especially in children) and the follicular exudate at the surface of the crypts The appearance of the throat is dependent upon the type and severity of the infection Peritonsillitis is usually present and pharyngeal myositis accounts for dysphagia The organism most often responsible for the infection is *Streptococcus hemolyticus* although staphylococci and mixed infections are frequently found If possible tonsillar cultures should be obtained especially in children

Complications

The *complications* of acute tonsillitis are varied and include peritonsillar abscess tonsillar abscess parapharyngeal abscess toxemia septicemia and pyemia endocarditis arthritis acute otitis media suppurative cervical adenitis and cellulitis perinephric abscess and acute nephritis

Treatment

The treatment is the use of the antimicrobial agent specific for the predominant bacteria Three hundred thousand units of procaine penicillin intramuscularly daily for four to five days or 0 25 Gm of chloramphenicol taken every three hours for three doses then every six hours for four to five days will suffice to control the infection A soft diet is recommended for the first day or two or until the dysphagia has been reduced For discomfort in the throat and neck one of the acetylsalicylic acid derivatives 0 35–0 65 Gm every two to three hours should be prescribed Occasionally 30 mg of codeine or 10–15 mg of morphine may be necessary An ice collar is of value during the first day or two Diphtheria Plaut Vincent s angina and scarlet fever warrant consideration when membrane formation occurs (Table 52) Of less frequent occurrence, but not to be disregarded, are syphilis (all stages) tuberculosis blood disturbances (such as malignant neutropenia or infectious mononucleosis) herpes pemphigus, erythema multiforme thrush septic sore throat lichen ruber planus leukoplakia and carcinoma

Secondary Tonsillitis

The diagnosis of tonsillitis is made too often in children Even when the classical signs and symptoms of tonsillitis appear including what seems to be an exudate process in the crypts and the tonsils are enlarged and reddened these tonsillar changes may be merely those which accompany the usual respiratory infections and are to be considered a secondary rather than a primary manifestation The use of the antibiotics would be premature and possibly unnecessary for experience has been that this type of respiratory disease with secondary tonsillar manifestations runs the usual course of five to ten days in spite of rather heavy medication used

Treatment Active management consists of absolute rest in bed light diet and general supportive and eliminative measures The salicylates are frequently of benefit Antimicrobial therapy may be judiciously and effectively employed Cold applications to the neck are appreciated by the patient Early topical application to the tonsils of a solution of nitrate of silver (5 per cent) or guaiacol (25 per cent in olive oil) frequently relieves the pain The crypts may be irrigated with hydrogen peroxide or sucked out through a cannula Administration of a saline laxative at the outset assists in relieving the general toxic state If these measures prove effective no pseudomembrane is seen after the first or second day Ordinarily, the disease runs its course in three to five days Gargles are much less effective than antiseptic sprays

TABLE 52 DIFFERENTIAL DIAGNOSIS OF MEMBRANOUS TONSILLITIS

	Foll cular tons ll t s	D phtheria	Plaut V incent s angina	Scarlet fever
Onset	Sudden often ushered in with chill	Insidious seldom chills	Ins dious	Sudden with sore throat and ch lls
Temperature	High (101° 105° F)	Low (99° 100° F)	Seldom elevated	High
Constitut onal symptoms	Constitutional de pression not marked usually in proportion to temperature face is flushed pulse full and bounding	Const tutional de press on is great pulse slow and compressible pale face vomiting fre quent at onset albuminuria fre quent	Very little con stitut onal dis turbance	Beg ns w th chills and vomit ng w th a rash in 12 to 36 hours strawberry tongue and prostration
Pain	Pa n on swallowing	Little pain	Not marked	Very marked dif ficulty in swal low ng
Adenit s	Enlarged submax illary nodes on both sides but not marked	Glands involved on both sides swollen and tender	Retromand bular adenopathy	Neck tender but glands have tend ency to swell later in course
Locat on of membranes	Discrete spots on tons ls also on other lympho d tissue	Not limited to tonsil but rapidly spreads to involve other parts including the tongue buccal mucosa and lips	Usually unilateral on tonsil	May be any place in the pharynx
Type of mem brane	Exudate thin white or yellowish is not adherent or confined to the tonsil does not bleed or reform rapidly or exten sively	Membrane adherent d rty gray or deep yellow bleeds on removalandreadily reforms even to a greater degree foul pecul ar odor to breath	Dirty gray mem brane not a true membrane but necros s of epi thelium leaving a superficial ulcer with an irregular border	Thin membrane on a phlegmo nous cyanotic appearing mucosa
Smears	Streptococcus staphylococcus and pneumoco ccus	Smears and culture show Klebs Loffler bacillus	*B fusiformis* and *sp rorefr ngens*	Usually reveal hemolyt c strep tococci (beta type)

a local or general infection caused by a pathogenic agent Tonsillitis is frequently the local manifestation of a more general disturbance which has its original focus in some part of the upper respiratory tract

The treatment of the sore throat de pends on its cause Throat lozenges should be interdicted or judiciously em ployed There might be psychologic value to the patient of some pleasant tasting lozenge held in the mouth but the wide spread dosing with lozenges concocted of all varieties and types of antibiotics is un doubtedly establishing sensitivities to the medication and producing a disagreeable pharyngeal condition as the result of moni liasis The mucosa of all orifices are capable of causing general systemic sensitization Experience also has shown that local ap plication of antibiotics whether by lozenge or by inhalation frequently incites the de velopment of a stomatitis However ad ministration of antimicrobials parenterally may be most effective

unless recovery is certain and incontrovertible prior to that time Recurrences are treated in the same manner the incision again made and spread widely with the forceps It is possible that the pus may become loculated and recurrence likely unless complete drainage is established

MEMBRANOUS PHARYNGITIS

Membranous pharyngitis (white or pseudomembranous angina) is a general term implying any one of a number of disease entities Each has a definite pathologic as well as bacteriologic differentiation although clinically they more or less resemble one another The following is a convenient classification

I Septic sore throat
II Plaut Vincent s angina (ulceromembranous)
III Diphtheria (membranous)
IV Blood disturbances
  A Malignant neutropenia (agranulocytosis)
  B Pernicious anemia
  C Acute leukemia
  D Infectious mononucleosis
V Pseudomembranous
  A Scarlatina
  B Measles
  C Pertussis
  D Erysipelas
VI Pneumococcus
VII Locally induced
  A Escharotics
  B Operations
  C X ray
  D Radium
VIII Syphilis and tuberculosis

Plaut Vincent s Angina

Plaut Vincent s angina is an *infection of* the pharyngeal *mucous membrane* by fusiform bacilli and spirochetes which are mutant forms of the same microorganism Generally beginning *on* the tonsils a pseudomembrane extends to the surrounding parts The alveolar process tooth sockets bronchial mucous membrane and even *other parts of the body* may be attacked The organisms are autoinoculable The disease may be associated with diphtheria *syphilis streptococcus or staphylococcus* infection or dental involvement

The subjective symptoms are usually *those of sore mouth metallic taste pain* sensitive teeth mental depression bleeding gums salivation lassitude pharyngitis headache earache nasal discharge, and gastrointestinal disturbances The breath is foul especially with sloughing ulcers are *present the throat painful on swallowing* and there is generally some swelling of the submaxillary lymph nodes *There often is* an associated history of gingival bleeding with or without brushing of teeth There *may be fever up to 102.5° F The tongue* is furred and swollen Vesicles break down and ulcerate

The disease differs from acute pharyngitis of streptococcic or staphylococcic origin by being less severe and usually by a lack of constitutional symptoms There is a fetid breath a tendency to ulcerations and a preponderance of characteristic *fusospirochetal organisms* in the dirty bluish gray membrane

Plaut Vincent s angina must be differentiated from diphtheria syphilis tuberculosis malignant disease pyorrhea blood disturbances (malignant neutropenia *pernicious anemia* acute leukemia) and other conditions in which membranes and ulcerations are present in the mouth and pharynx The *infection occasionally* coexists with one or more of these conditions

Treatment Treatment is by means of *procaine penicillin* 600 000 units intramuscularly for two to three days or until the necrotic ulcer has healed *Inadequate treatment may cause* a *chronic* Plaut Vincent s infection of the tonsil as well as chronic gingivitis and periodontal disease

PERITONSILLAR ABSCESS

Peritonsillar abscess appears forty-eight to seventy two hours after the acute sore throat episode has subsided The acute tonsillitis results in abscess formation from extension of the process in the loose peri tonsillar tissue The condition usually occurs in the colder months of the year Children under six years of age are seldom affected While the process ordinarily is unilateral it may at times be bilateral espe cially in influenza It is not uncommon for a patient to have experienced previous at tacks of peritonsillar abscess

In the vast majority of patients the abscess forms in the superior and lateral part of the tonsillar fossa behind the fibrous layer of the structure the posterior inferior portion being more or less infiltrated This infiltration produces blockage of the venous return at times leading to marked edema of the uvula As the condition progresses extension takes place laterally with infiltra tion of the pterygoid muscles giving rise to trismus (lockjaw) at the height of the proc ess Spontaneous rupture of an abscess oc casionally takes place

The early symptoms are those of acute tonsillitis Later there is marked difficulty in swallowing and the face will have an anxious appearance There is a nasal twang to the voice and the patient speaks as though he had a mouth full of hot pota toes Relative immobility of the jaw trismus and neuralgia add to the suffering The tongue is thick and coated there is also fetor ex ore due to the inability to maintain a satisfactory mouth hygiene The temperature is usually within low limits (99° 100° F) The general symptoms are characteristic of lack of nourishment sleep lessness and continuous pain so that the patient becomes exhausted

It is difficult to obtain a view of the pharynx because of inability to open the jaw The involved side is pushed forward and medially to the midline The mucous membrane appears reddened and wrinkled The uvula is pushed over to the normal side and sometimes becomes so edematous as to extend down onto the tongue The tonsil itself is hidden by swelling of the pillars faucial landmarks are obliterated A fibrinous exudate is present the lacunae being filled Fluctuation is evident in forty eight hours usually in the superior external portion of the palatoglossal fold The course varies from four to ten days Palpa tion at first elicits firmness which later changes to softness

The condition must be differentiated from various affections of the mucous mem branes types of pharyngitis and swellings in the region of the tonsil especially diphtheria peritonsillitis primary or ter tiary syphilis tumors and aneurysms of the internal carotid artery

Complications

Septicopyemia thrombosis or gangrene of the extremities lung abscess and severe hemorrhage following spontaneous rupture or incision are the most feared complica tions of a peritonsillar abscess Endocranial involvements such as edema cavernous sinus thrombosis brain abscess (temporal lobe) meningitis and osteomyelitis of the sella turcica have been known to occur

Treatment

Treatment of a peritonsillar abscess is immediate use of high initial doses of the antibiotics with incision and drainage of the supratonsillar area by bistoury making certain that the incision extends from the upper margin of peritonsillar edema down to the anterior pillar just medial to the third molar The incision should be spread with hemostatic forceps to be certain that the pocketed pus is released The antibiotics should be continued for at least one week for recurrences are common if the drainage or medication is inadequate The patient must be kept at home for at least a week

heterophile antibody serum response The treatment in infectious mononucleosis is symptomatic Lymphosarcoma lymphoma the purpuras, and leukemias may make their first appearance in the pharyngeal tonsils

TONSILLECTOMY AND ADENOIDECTOMY

Surgical removal of tonsils is the treatment of choice in repeated proved cases of tonsillitis or peritonsillar abscess When actual pus can be demonstrated in the tonsillar parenchyma as differentiated from the epithelial debris tonsillectomy is indicated *In some children the tonsillar hypertrophy* becomes so great that actual mechanical obstruction to the upper airway becomes a major factor and the tonsils must be removed In this case size alone may be the determining factor for surgical intervention It should be emphasized that tonsillectomy as a surgical procedure carries with it risks of morbidity and mortality It should not be used as a cure all for the common childhood ailments and certainly never recommended as a prophylactic measure

A concerted educational effort has been made to unfetter the medical world from the ritualistic surgical approach to the removal of tonsils and adenoids by pointing out certain fallacies in the indications for removal Actually the tonsil is a useful organ especially in the younger child it plays a major role in autovaccination and as a body defense mechanism Tonsils in children under 6 to 7 years of age should not be removed except in extreme circumstances If antibiotics and chemotherapy usually help to curtail the secondary infections they should be employed for the primary ones Removal of large uninfected tonsils for prophylactic or other reasons is not only valueless but actually detrimental to the patient To brand a tonsil as infected merely because of its size is erroneous and a gross misconception The focal infection theory is not generally accepted. It has not been established that tonsillectomy cures or prevents disease Allergy must be accorded adequate consideration In this connection it is strongly urged that tonsillectomy be avoided when allergy is present except when absolute indications exist The allergic state should first be investigated and treated adequately The relation of tonsillectomy to the cause of poliomyelitis is interesting but highly controversial However it is very desirable to postpone an 'elective procedure during periods of epidemics

'LUMP' IN THE THROAT

If after careful history physical examination and necessary laboratory studies the physician feels he is dealing with so-called 'globus hystericus he should reassure his patient that there is no cancer or venereal disease and perhaps recommend a mild sedative (phenobarbital) for four to five days He should not swab the throat or perform any pharyngeal procedure that will fix the symptoms to cause further concern to his patient This symptom is a common psychosomatic manifestation, usually self limited and greatly helped by the understanding counsel of the physician

LARYNGITIS

Most forms of laryngeal disease have many symptoms in common as manifested by interference with essential functions—phonation respiration and deglutition When the position of the larynx in the structural framework of the neck its lymphatic and nerve supply are considered it is comparatively simple to visualize the multitudinous variety of acute and chronic inflammations disturbances of innervation and changes as the result of external as well as local and systematic factors that are capable of affecting this organ

Blood Disturbances of the Pharynx

It is not unusual for patients with a blood dyscrasia to have the first symptom of the disease manifest itself in the mouth Findings of pallor of the mucous membrane, enlargement of lymph nodes, hemorrhage into the tissues or from the mucous membrane surfaces, or ulcerative lesions in this area should direct suspicion to a possible blood disturbance The anginas are capable of producing four types of changes in the blood (1) polymorphonuclear leukocytosis (follicular tonsillitis and septic throat) (2) mononuclear leukocytosis (infectious mononucleosis), (3) leukopenia with a decrease of granulocytes (agranulocytic angina and pseudoagranulocytic angina), and (4) leukocytosis with a relative hypogranulocytosis acute lymphatic leukemia, and acute lymphadenosis (generalized Plaut Vincent s infection)

Cervical Lymphadenopathy

The most common causes of localized lymphadenopathy are acute and chronic infections of the head and neck Infections of the ear, nose, mouth, and throat lead to a chain of small, discrete at first soft, later hard nodes in the anterior or posterior cervical region either unilateral or bilateral The submaxillary sublingual and postauricular lymph nodes are also variously involved While blood examination usually reveals no signs of an anemia in the acute state the white count is elevated and shows a preponderance of granulocytes with various degrees of shift to the left Some infectious diseases produce a leukopenia Malaria typhoid fever pertussis tuberculosis, and syphilis which may also have associated with it an enlarged spleen, can react with an increase in the number of lymphocytes

Proper identification of a mass in the neck is of utmost importance If a diagnosis is not made the patient is subjected to unnecessary worry and the loss of valuable time for surgical interference or medical therapy Patients may complain of a generalized or local swelling yet the physician can discover no abnormal mass In such instances the patient may mistake a normal structure such as the hyoid bone for a swelling or occasionally may be able to palpate a mass before it is discernible to the examiner Fear of cancer, goiter, or mumps often causes apprehension and self palpation Almost every patient can recall some trauma, which may or may not be related to the mass in the neck While it may be a hematoma, branchial cysts often follow an injury or even excess straining The sudden appearance of a swelling with fever and malaise should suggest infectious lymphadenitis due to infectious mononucleosis, measles, scarlet fever, diphtheria, tonsillitis, and other upper respiratory diseases Before exploring a neck swelling surgically, or treating it with x ray, a diagnosis must be made These masses can usually be differentiated by careful examination, beginning with physical and proceeding through laboratory and histologic diagnosis

The majority of tumors of the neck require surgery Those of a malignant character are treated by a combined surgery, electrosurgery and irradiation Inflammatory processes are treated medically to the stage of suppuration when surgery becomes necessary for drainage Constitutional affections and specific infections require systemic treatment in addition to the care of the local process

The tonsils being lymphoid structures reflect changes that occur in the lymphatic organs Frequently the first symptoms of infectious mononucleosis are dysphagia and exudative tonsillitis The observation has been made, however, that the dysphagia is out of proportion to the tonsillar findings and the blood smear will reveal the lymphocytosis and mononucleosis Further confirmation is obtained by the

efforts on relieving the general or specific causes of tension, being aware of the possibility of psychiatric consultation Paresis or paralysis of one or both of the vocal cords (except for bilateral abductor paralysis) can be treated only by specific measures of rehabilitation in which a change of vocation may be necessary, voice exercises should be carried out in an attempt to use whatever functions remain In bilateral cordal paralysis several surgical procedures have been devised to pull one arytenoid and vocal cord to one side Emergency care may call for an immediate tracheotomy to relieve respiratory distress

TRACHEOTOMY

The various conditions in whic operation is indicated may be divide four groups (1) A morbid process su edema paralysis, and malignant d which suddenly or gradually reduces laryngeal lumen and involves the pr bility of asphyxia (2) Physiologic rest wh tends to reduce the activity of the mor process and delay its progress such as lary geal tuberculosis and syphilis (3) Impa tion of a foreign body that cannot b removed through the glottis (4) Facilitation of contemplated laryngeal surgery by a preliminary opening into the trachea

TABLE 53 DIFFERENTIAL DIAGNOSIS OF SUDDEN DYSPNEA IN CHILDREN

	Laryngeal stridor	*Foreign body*	*Edema of larynx*
Age	Usually in young children	Swallowed or aspirated at any age	Any age but not usually in the young
Site	A glottic closure by spasmodic adduction	Nothing observed in pharynx unless some manipulation has been attempted glottis or esophagus	Swelling is in larynx itself One or all parts of larynx may be involved
Onset	Symptoms usually come on at night while child is asleep awakes suddenly gasps for breath and shows every evidence of prompt suffocation without cough or hoarseness a few gasps and a quantity of air is drawn in to the lungs with a crowing sound and the respiration again becomes normal	Symptoms come on abruptly and much of the response is dependent upon size character, and location of the foreign body there is no fever unless infection occurs	Hoarseness, even aphonia shortness of breath
emarks	A form of false croup of noninflammatory character a reflex which affects the adductor muscles due to adenoids intestinal parasites and indigestion possibly precipitated by nervous shock or excitement before retiring patients may hold their breath long enough to become cyanotic and present an alarming picture	Following a history of having played with a foreign body which disappeared then sudden spasms of coughing choking often followed by cyanosis and alteration of voice	Comes on rather suddenly may be inflammatory or noninflammatory if it follows infectious disease it is of sudden onset with dyspnea
nent	Relief obtained by alternately stimulating body with heat and cold attack almost always subsides spontaneously without any after effect	No particular position will give relief but head may be kept motionless if foreign body is sharp X ray will disclose its presence by radio opaque removal of foreign body affords relief	Head is usually flexed forward and shoulder muscles are used in an effort to breathe lifting the head does not relieve the distress

Hoarseness is defined as roughness or discordance in the quality of a voice The voice is influenced by either an alteration of its pitch or its intensity or of both Hoarseness as a symptom is usually grouped into two general, all inclusive classes on the basis of pathogenetic factors alone (1) those changes which influence the voice (either intensity pitch, or quality) without a pathologic process in the larynx itself, and (2) those locally acting causes which produce the hoarseness by a lesion within or directly external to the laryngeal chamber

There are numerous congenital anomalies and deformities of the larynx which are manifest at birth As man progresses through life, there is perhaps no organ, by virtue of its position and function which is subject to greater abuse or mistreatment The term laryngitis refers to an acute or chronic inflammatory condition of any part of the larynx interfering with normal respiration or phonation There are in addition noninflammatory conditions which similarly may affect the larynx these being mainly disturbances of its innervation

No treatment should be undertaken for hoarseness until the cause is established and this can be done only by visualization of the larynx, either indirectly by mirror or directly by the laryngoscope The most common causes of hoarseness are due to (1) respiratory infections including the common cold and sinusitis (2) benign tumors and polyps (3) carcinoma, (4) tuberculosis (5) syphilis (6) excessive use of the voice or inability to use the larynx properly because of emotional tension or psychogenic disorder and (7) paresis or paralysis of one or both vocal cords

Acute and chronic inflammatory dermatoses comprise a large number of conditions in which the larynx becomes affected (exudative laryngitis) Diseases of the hematopoietic and lymphatic systems such as anemia chlorosis pernicious anemia malignant neutropenia, leukemia purpura, and scurvy often are complicated by laryngeal manifestations Laryngeal disorders occurring in the course of systemic disease (symptomatic laryngitis) has been observed in the contagious and infectious states such as measles, smallpox, chicken pox, scarlet fever, erysipelas typhoid fever, pertussis, influenza, and diphtheria

In diagnosis of laryngeal disease the following program has been found helpful

1 Complete case history,
2 Indirect laryngoscopy,
3 Complete general physical examination particularly of the upper respiratory tract,
4 Roentgenologic studies of the sinuses chest, and neck,
5 Blood examination, both microscopic and serologic
6 Examination of the sputum,
7 Direct laryngoscopy, bronchoscopy or esophagoscopy
8 Biopsy

Hoarseness associated with acute laryngitis due to respiratory infection should be treated by (1) voice rest for two to three days (2) the use of ammonium chloride as an expectorant (0 33 Gm in syrup of citric acid) (3) steam inhalations with or without tincture of benzoin for twenty minutes every three hours Benign tumors and polyps are to be removed under direct vision Carcinoma of the larynx calls for a variety of surgical approaches (laryngofissure or laryngectomy), depending on the type, location and involvement of surrounding structures Tuberculosis of the larynx should be treated in conjunction with the existing pulmonary lesions and at present shows excellent response to the use of streptomycin therapy Syphilis of the larynx is treated the same as syphilis of any other part of the body * When a diagnosis of hoarseness due to emotional tension is made the clinician should concentrate his

* See Chapter 39

must be performed and an oxygen and carbon dioxide mixture should be administered During the procedure bleeding may be troublesome and alarming Temporary control may be effected by packing gauze firmly into the wound and around the cannula As soon as it can be accomplished, ties or sutures should be employed to secure hemostasis

Silver tubes are preferred when the instrument is to be worn a long time aluminum tubes are more suitable when they are to be removed within a brief period since the metal is corroded by the secretions Age and sex are determining factors in the choice of the size of tube To prevent tubes from becoming dislodged they should be carefully tied with tape around the neck

An important point is to keep the cannula as free as possible from the copious discharges which are formed for a few days after tracheotomy Granulations which form at the external tracheal orifice and in the trachea itself should be kept down with astringent solutions such as silver nitrate

Before the cannula is permanently withdrawn the natural breathing powers of the patient should be tested by closing the aperture of the tube with a stopper secured by silk If the patient can breathe without difficulty the tracheotomy tube is withdrawn but kept within easy reach with the pilot in position for a possible emergency As a rule however reinsertion is not required the wound closes up after a few days and heals completely within a week or two

FOREIGN BODIES

All types sizes and shapes of foreign bodies have been swallowed or inhaled by infants children and adults *The diagnosis* is made by a history obtained from parents or the patient a description is given of the foreign body and the episode associated with the ingestion Sometimes however there may be no recollection of the incident or the foreign body, later there may be a cough asthma, hoarseness or even hemoptysis if the foreign body has descended to the lower respiratory tract below the laryngeal orifice Initial symptoms are coughing choking wheezing and dyspnea Generally the initial spasmodic symptoms are followed by a period of quiescence during which little or no evidence of a foreign body is manifest It becomes fixed and the acute irritation to the bronchus which causes cough disappears With the onset of infection one of a number of phenomena takes place depending upon the degree of obstruction that the foreign body effects If it is possible for air to pass freely into and out of the lung beyond the point of obstruction the only symptom will be that of an inspiratory and expiratory wheeze as the air passes the object

If swallowed the symptoms later may be dysphagia chest pains and even fever and neck or back symptoms if there has been esophageal perforation with mediastinitis

Foreign bodies of long standing give signs and symptoms which simulate pulmonary tuberculosis

Complete obstruction of the bronchus causes the air to become absorbed beyond the point of obstruction with the typical picture of atelectasis It may also give rise to signs and symptoms of pneumonia or of an emphysema (drowned lung) The distinguishing feature is the marked decrease in size of the lung distal to the point of obstruction compensated for by a shift of the heart toward the involved side and an elevation of the leaf of the diaphragm on the same side

A foreign body lodged in one bronchus may shift its position on cough and cause a *complete change in symptoms* and physical findings within a very short time

A carefully taken history is of the utmost importance It is occasionally the only posi

Intubation should be tried before tracheotomy, unless it is contraindicated On the other hand tracheotomy in infants conserves the larynx better than does intubation Although tracheotomy is safer, the operation is nevertheless a surgical procedure carrying with it certain risks Actually there is no contraindication to tracheotomy and the operative mortality is most commonly attributable to unnecessary delay in its performance improper technic and inefficient aftercare

Obstructive Lesions of the Larynx

The diagnosis of obstructive lesions of the larynx is arrived at by direct and indirect inspection of the larynx the general physical signs and the roentgen ray findings The outstanding signs and symptoms of obstructive laryngeal dyspnea are inspiratory retraction of the supraclavicular, suprasternal intercostal and epigastric spaces Stridor wheezing restlessness and cyanosis (the sign of impending asphyxiation and cardiac failure) soon follow Since the differential diagnosis is frequently difficult especially in children Table 53 may be of interest

With the recognition of the value of tracheotomy in the treatment of the anoxia associated with the bulbar type of anterior poliomyelitis has come an increased awareness of the necessity of treating the respiratory obstruction occurring in other diseases such as tetanus cerebral vascular accident brain traumas etc It is now realized that the actual cause of death in such cases is not the disease or injury but rather the anoxia resulting from upper respiratory obstruction

The principle of tracheotomy is the establishment of an adequate airway when because of disease or injury the pharyngeal or laryngeal musculature is unable to perform the functions of swallowing and inspiratory expiratory control Clinical cyanosis need not be apparent for anoxia to be present An anoxia may be manifest only in such symptoms and signs as apprehension, restlessness, irritability, vasomotor flushing Anoxia if prolonged over hours or days, may initiate destruction of central nervous system tissue with subsequent loss of vital functions and even death

Tracheotomy is one surgical procedure with which every practitioner should be familiar It may be life-saving in acute asphyxia, but should also be considered therapeutic for the treatment of chronic anoxia in the diseases and conditions mentioned All practitioners should carry a scalpel and a set of tracheotomy tubes in their kits When the physician recognizes an acute asphyxia, due to upper respiratory obstruction, he should make the incision halfway between the suprasternal notch and the thyroid notch The head should be held with the chin pointed to the ceiling In cerebral trauma cerebral vascular accidents acute tetanus bulbar poliomyelitis the physician should recommend tracheotomy as part of the general treatment where anoxia exists and is increasing

Tracheotomy should be done whenever possible before the patient is moribund Depending upon the etiology, tracheotomy may be performed tranquilly or as an emergency measure The site of choice is between the second third and fourth tracheal rings

Technic of Tracheotomy

The notch of the thyroid cartilage (Adam s apple) is the important landmark An incision is made from this notch to above the suprasternal notch It is carried through the skin and subcutaneous tissues The two rings of the trachea are easily felt as corrugations by palpation along the Adam s apple over the cricothyroid membrane The knife then is used to make a vertical incision and the lips of the tracheal wound spread apart with a dilator If respiration has ceased artificial respiration

Dysphagia

The most significant symptom of esophageal disease is dysphagia When this symptom becomes progressive the presence of an organic obstructing lesion is suggested The symptom of difficulty in swallowing should be evaluated from the point of view of esophageal disease the practitioner should be aware of the time of onset duration the development of difficulty in swallowing solid foods and the related symptom of substernal distress or burning Another important diagnostic symptom is regurgitation of food Weight loss occurs gradually in the early stages of esophageal carcinoma and may be overlooked When it becomes manifest the neoplasm may be well established Visualization of function and changes in appearance of the esophageal mucosa should be done with roentgen ray and fluoroscopy Although there may be a lack of positive findings direct visualization and biopsy by means of the esophagoscope should be employed Hasty endoscopic examination is seldom necessary, and in most instances it is recommended only after all other diagnostic procedures have been exhausted

The symptom of dysphagia may indicate the presence of a disease other than neoplasm but only an unremitting diagnostic survey will establish a diagnosis Pharyngeal and esophageal diverticulum is an occasional finding in dysphagia It is revealed in the roentgen ray fluoroscopic or direct esophagoscopic procedures Cardiac enlargements aortic changes due to syphilis, and encephalitides involving the brain stem (associated with a defect in speech characterized by a nasal quality) all may cause difficulty in swallowing The subjective symptoms are pain which is either constant or present only on swallowing (odynphagia) and disturbances in swallowing (dysphagia) Symptoms arising from hyperactivity as reversed peristaltic movements comprise a complex commonly seen in psychopathic states

tive diagnostic feature after the initial symptoms have subsided and before the signs of complications manifest themselves A complete roentgen examination should be made The completed study should include a fluoroscopic examination of the chest Lateral films are indispensable

The presence of a foreign body enters into the differential diagnosis of all causes of hoarseness and laryngeal obstruction Direct or indirect examination is indicated in any case under suspicion although roentgen rays are occasionally negative

In an emergency when the foreign body descends the lower respiratory tract or is held in the laryngeal space and asphyxia ensues tracheotomy should be done immediately as a life saving measure When time is not an immediate factor thorough roentgen ray and fluoroscopic studies must be made to find the approximate location and to allow for proper planning of the endoscopic maneuvers and the assembly of proper equipment Nonopaque foreign bodies present a special problem in diagnosis and localization Here the value of experience is paramount

ESOPHAGUS

The esophagus is prone to congenital deformities arising from derangements during certain phases of its development It is also affected by a number of neurogenic and psychogenic conditions the latter being observed more commonly in the female sex Some diseases are systemic or metastatic in origin In the latter instances they originate particularly in abdominal and thoracic viscera Infections and malignant neoplasms arising in the neck thorax and abdomen also spread by contiguity of structure invading either the outer or all of the layers of the esophagus Finally the esophagus is subject to local affections peculiar to its structure Often these affections are not manifested clinically lipomas may not be disclosed until they are advanced as is often the case in carcinoma Also the esophagus is subject to direct trauma by ingested corrosive substances or penetrating wounds of the neck, thorax and abdomen

Foreign Bodies

There are three normal narrowings which constitute the usual sites of lodgment of foreign bodies in the esophagus First at the upper thoracic aperture immediately below the cricopharyngeus muscle The second normal narrowing of the esophagus is at the level of the arch of the aorta The third site is the beginning of the cardia at the hiatus of the diaphragm and constitutes the second most common location in the lodgment of the foreign bodies (relatively few remain there once they have passed the upper thoracic aperture)

The initial symptoms of a foreign body in the esophagus are frequently identical to those of a foreign body anywhere in the air or food passage choking coughing gagging dyspnea and cyanosis Pain is usually located at the level of the thyroid cartilage It may radiate back between the shoulder blades if the foreign body lodges near the cardia It is possible to have a foreign body lodged in the esophagus without symptoms of any type until signs of obstruction or infection ensue Respiratory symptoms are occasionally produced by foreign bodies in the cervical esophagus

Only one method is safe enough to be considered for removal of foreign bodies in the esophagus—esophagoscopy with the lumen of the esophagus always visible To push the foreign body blindly into the stomach causes laceration of the esophagus The short delay required to plan the procedure is not dangerous while hurried esophagoscopy performed with inadequate instruments or preparation of the patient may be fatal

the eyes closed When aqueous solutions are used, and if the conjunctiva is being treated, the lower lid is everted and the drop placed in the lower cul de sac with the patient looking up If it is desirable for the drug to be absorbed or to reach the interior of the eye, the patient should be instructed to look down, with the upper lid held up the drop is placed directly upon the cornea It is essential for the dropper not to touch the eye, especially if the physician is instilling the drops from a stock or office bottle, as many infections, especially epidemic keratoconjunctivitis, have been transmitted in this way from one patient to another

Drugs which have an unpleasant taste or whose general absorption is not desired (such as atropine) may be prevented from entering the nose through the lacrimal passages if the physician, or patient, will hold the nose at the inner canthus for two or three minutes after instillation Occasionally instead of solutions and ointments, small gelatin discs or wafers containing drugs are applied to the conjunctival sac However, this method is no longer widely used, since it is less convenient and less readily available

In addition to the instillation of solutions and ointments, the direct application of drugs is at times necessary, especially in the treatment of corneal ulcers This is best done by tightly wrapping a very small wisp of cotton on a fine metal applicator or, best of all, a toothpick which has been whittled to a sharp point The end of the cotton is cut off with scissors, leaving a fine tipped cotton applicator which can be dipped in the acid or other medicament to be used the excess of drug is shaken or wiped off so that when the cornea is touched with the tip no excess is spread over the cornea or conjunctiva only the desired area thus being treated

In the treatment of certain types of conjunctival disease it may be necessary to apply drugs directly to the conjunctiva by

to the upper and lower tarsal conjunctiva Silver nitrate 1 per cent, formerly used in this way in treating most forms of acute conjunctivitis but which is then neutralized by irrigation with isotonic solution of sodium chloride, has been largely superseded by the antibiotics However, it is still useful in some conditions

Irrigation of the conjunctival sac is indicated for the removal of secretion or debris and is best accomplished either by use of a special spray bottle which delivers the solution in a form of a fine spray or by use of an ordinary medicine dropper Eye cups are most unhygienic, as they wash dirt and bacteria from the lids into the conjunctival sac, and their use should be discouraged The best solutions for irrigation are normal salt solution (isotonic) and saturated boric acid solution They are most comfortable if used at body temperature In the absence of signs of disease or inflammatory processes routine daily irrigation of the eyes is superfluous as the normal lacrimal secretion serves to keep the eye moistened and cleansed

PARENTERAL INJECTION

This technic must be at times employed Subcutaneous injection of vaccines, staphylococcus toxoid, tuberculin, lens antigen, and other substances used for desensitization may be desirable Foreign proteins—especially typhoid vaccine—are administered by the intravenous route Penicillin and some forms of foreign protein may be administered by intramuscular injection Treatment of syphilitic eye disease is largely accomplished through the parenteral route

37. *Ophthalmologic Diseases*

WILLIAM A MANN

BEFORE any treatment of a diseased eye is undertaken it is absolutely essential to make an accurate diagnosis Should there be an error in diagnosis not only may the resultant lack of proper therapy result in eventual loss of visual function but improper treatment (such as the use of atropine in the presence of primary glaucoma which may have been erroneously diagnosed as iritis or the use of miotic therapy in a case of iritis mistakenly diagnosed as glaucoma) may actually aggravate the condition Occasionally even death may result as can occur when a malignant melanoma of the choroid is not treated by early enucleation of the eye but instead the secondary glaucoma is treated symptomatically Fortunately most eye diseases can be diagnosed with considerable accuracy by one who is skilled in methods of external examination ophthalmoscopy and laboratory methods Special procedures such as tonometric examination and slit lamp biomicroscopy are essential in certain cases to arrive at an accurate evaluation few physicians aside from well trained ophthalmologists will attempt to diagnose and treat such cases It may however at times be necessary for general practitioners to care for cases of ophthalmic disease as emergencies or in the absence of any available specialist This chapter has been prepared with the objective of assisting them in a rational approach to ocular therapeutics Discussion therefore is limited to the more commonly encountered eye conditions

Methods Employed in Ocular Therapeutics

TOPICAL APPLICATION

This is the commonest therapy employed in treating eye disease The administered drug may be in aqueous solution or in an ointment If it is the latter it usually is a petrolatum base containing 20 per cent hydrous wool fat An ointment remains in contact with the tissues longer than does a solution it usually is instilled in the conjunctival sac by expressing it from a small tube the tip of which is held just behind the everted lower lid but never touching it If however the ointment is prescribed for lid margin inflammation it is best applied with the tip of the clean finger to the lid margins of the upper and lower lids with

ALLERGIC BLEPHARITIS

This problem also is quite common It is characterized by redness edema of the skin of the lids, eosinophiles in the conjunctival scraping and is accompanied by considerable itching The most common causes are cosmetics (face powder and nail polish) and soap flakes Less common causes are animal dander, drugs house dust, and foods Treatment consists of removing the cause if possible and of giving symptomatic relief with antihistaminic drugs by mouth or locally in the form of, for example, antistine hydrochloride ophthalmic solution or a solution of procaine (0 5 per cent) and epinephrine (1 1000) as a 4 per cent solution (1 25 000) in distilled water One drop should be instilled into the conjunctival sac several times a day or as often as is necessary to relieve the accompanying itching

Cortisone acetate (cortone acetate) by local instillation is dramatically effective in relieving the subjective and objective signs of allergic manifestations in the lids and conjunctiva usually within a few hours It should be prescribed in from full strength (25 mg per cc) in severe cases to a 1 4 dilution with normal salt solution in less acute cases Instillation is made every hour until the eyes are free of objective igns then with gradually decreasing frequency until it is determined what minimal ose may be required This will carry the atient through the unpleasant period ile search as to the etiologic factor is ng pursued In some cases where it may be possible to find the allergen pro- ged local treatment may be necessary

CHRONIC MEIBOMITIS

This may be part of a chronic blep The contents of the meibomian should be expressed with pressure f glass rod or by pressing the thumb na the opposed lids Treatment of the ble ritis (as discussed above) must be car out at the same time It is usually neces to continue treatment for a considera period

HORDEOLUM

Hordeolum or stye, may appear during the blepharitis or with little evidence of preceding lid inflammation It should be treated with moist heat and then incised when it has 'pointed ' It should not be expressed by pressure To prevent recurrent hordeolum and to treat the underlying blepharitis, bacitracin, or sulfathiazole solution or ointment should be used in the eye several times a day, until there has been evidence of clinical cure of the chronic lid infection and it can be assumed that staphylococci are no longer present Eyestrain or allergy which results in rubbing the eyes and reinfecting the glands of Zeiss and Moll (site of the hordeolum) may be treated accordingly

CHALAZION

This is a frequent accompaniment o blepharitis and requires treatment of the underlying condition If the chalazion is acute it should be treated as a hordeolum the remaining granuloma being incised and curetted after the acute symptoms have subsided

ORAL ADMINISTRATION

This therapeutic approach is useful for prescribing salicylates, iodides sulfonamides, vasodilators vitamins and a host of other preparations which eventually reach the eye or other tissues that affect the eye, and which may be indicated for a specific eye disability

PHYSIOTHERAPY

Physiotherapy may be provided at times in eye diseases by use of iontophoresis diathermy, the galvanic current (electrolysis to destroy aberrant cilia) and the actual cautery Heat for ocular inflammation may be provided as dry heat obtained by use of an infrared lamp, or as moist heat which is obtained with frequently changed cloths saturated with hot water or hot boric acid solution Cold is most conveniently applied by filling a rubber glove with ice, the open hand end being tied and the glove placed directly over the closed lids Massage may be applied to the eye in glaucoma, especially after a filtering operation, it is best carried out by placing the tips of two fingers over the closed upper eyelid and gently pressing each down alternately

IRRADIATION

This form of therapy involves the use of roentgen treatment applied to the cornea or lids and when deeper therapy for malignancies such as retinoblastoma is required Radium is useful for lid and bulbar malignancies in early stages The use of roentgen ray and radium should always be accompanied by protection of the lens with a lead prosthesis otherwise radiation cataract may develop Beta radiation has been recently employed for many external ocular conditions and apparently its use does not lead to cataract formation if the gamma rays are sufficiently excluded

Diseases of the Lids

CHRONIC BLEPHARITIS

This condition which is characterized by redness and crusting of the lid margins and sometimes by ulceration is extremely common Because of its tendency to recur it usually requires prolonged treatment Treatment of the ordinary staphylococcus variety includes removal of the crusts several times a day if necessary, with a cotton tipped applicator moistened with isotonic solution of sodium chloride or saturated boric solution An occasional application with a cotton tipped applicator of 1 per cent silver nitrate is particularly efficacious While penicillin ophthalmic ointment (1000 units per Gm) is of great value it frequently will evoke an allergic response, and this antibiotic should be reserved for extremely refractory cases or those in which the infection is of a more serious nature Sulfathiazole ointment 2 per cent (or if well tolerated, 5 per cent) applied to the lid margins with the tip of the *clean* finger once or twice a day is advised, the treatment being continued for a short time after clinical evidence of cure If the patient proves sensitive to sulfathiazole, bacitracin ophthalmic ointment, an ointment of ammoniated mercury 3 per cent, or ointment of yellow oxide of mercury 1 per cent may be substituted In extreme cases staphylococcus vaccine or staphylococcus toxoid may be employed If these are not successful roentgen therapy may be employed cautiously by someone trained in its use The globe must be protected of course with a lead prosthesis

guard against its transmission to others Use of silver protein preparations such as argyrol is largely obsolete Excessive and prolonged use of these substances lead to deposits of silver in the tissues (argyrosis)

EPIDEMIC KERATOCONJUNCTIVITIS

There is no specific treatment for this condition except the use of convalescent serum It is not affected by the antibiotics with the exception of aureomycin, terramycin, or chloramphenicol solution These are effective in about half the cases Strong treatment should be avoided The conjunctival sac may be irrigated with normal saline at frequent intervals Atropine 1 per cent should be instilled daily when corneal complications arise

ANGULAR CONJUNCTIVITIS

This is caused by the Morax Axenfeld bacillus and is characterized by roughening and excoriation of the inner or outer canthus It may be treated specifically with zinc sulfate or chloride, 0 2 per cent solution every two or three hours Usually chronic, it may be necessary to undertake treatment for a considerable period Treatment should usually be continued for several weeks after apparent cure Zinc oxide ointment U S P may be applied several times a day to the excoriated skin

INCLUSION BLENNORRHEA

Inclusion blennorrhea is seen most commonly in infants, and is best treated with sulfanilamide, 100 mg per Kg body weight

TRACHOMA

Trachoma is the most serious form of chronic conjunctivitis and while only occasional cases are seen in many regions, in certain portions of the world it is extremely common Because corneal involvement may cause blindness its early treatment is extremely important Intensive and wide spread treatment of the infected populace could result in practical eradication of the disease, as has been demonstrated by the Trachoma Clinics of Southern Illinois In the active stage of the disease sulfonamide therapy should be instituted and continued for two weeks or until the cornea is free of the subepithelial and punctate epithelial infiltrates Sulfanilamide should be prescribed to cause a blood concentration of only 3–5 mg per 100 cc Local sulfonamide therapy to the conjunctival sac is chiefly of benefit in combating secondary infection and should not be relied upon exclusively Aureomycin has also been used with some success in the treatment of trachoma

The classical local treatment of the disease, which is still useful, consists of the application of a stick of copper sulfate to the affected conjunctiva after the instillation of a local anesthetic, for example "pontocaine hydrochloride,' 0 5 per cent 'butyn sulfate,' 2 per cent, or 'holocaine *hydrochloride,' 2 per cent, followed* by irrigation with isotonic solution of sodium chloride This is repeated daily or every other day during the acute stage and may be supplemented by prescribing drops of 0 5 per cent copper sulfate solution with about 25 per cent glycerin in the aqueous mixture If this is not effective it may be necessary to express the follicles and then apply the copper stick The cicatricial stage of the disease may require surgical treatment

Particularly apt to become chronic are the forms of conjunctivitis due to the staphylococcus and Morax Axenfeld bacillus The latter, previously mentioned as angular conjunctivitis, is specifically treated with zinc, and the former, with which a blepharitis is frequently associated should be treated with sulfathiazole, sulfacetamide or chloramphenicol ointment locally and possibly toxoid parenterally (for example *Lederle s Toxoid, Dilution No 2, in* dosage from 05 cc increasing to 1 cc, the injec

Diseases of the Conjunctiva

ACUTE CONJUNCTIVITIS

This condition is usually of bacterial origin and it is advisable first to examine a conjunctival scraping to determine the offending organism Because of a tendency to invade the intact cornea and produce panophthalmitis the gonococcus causes the most serious form of conjunctivitis and this infection must be energetically treated Proper use of the Crede method of prophylaxis at birth has greatly reduced the incidence of gonococcal infection of the eye in the newborn, but it and gonococcal conjunctivitis in the adult are still occasionally seen * Frequent irrigation of the eye with normal salt solution, as often as every fifteen minutes if the discharge is profuse, is important to keep the secretions out of the conjunctival sac and away from the cornea Penicillin is probably the best antibiotic for this infection and a solution of penicillin 1000 units per cc, should be instilled every five minutes until there is no discharge Then it may be administered at hourly intervals, with simultaneous parenteral injections The uninvolved eye should be protected with a transparent shield which can be prepared from an X ray film properly cut, fitted and sealed with adhesive tape Foreign proteins (intramuscular injections of milk in infants or typhoid vaccine in adults) are a valuable adjunct to treatment

Other forms of acute conjunctivitis may be due to the pneumococcus organism Koch Weeks bacillus and more rarely the streptococcus staphylococcus diphtheria bacillus meningococcus and other organisms Local antibiotic therapy has proved most efficacious in treating these infections, except for the diphtheritic variety which requires of course, antitoxin Choice of the antibiotic to be employed depends to some extent upon the particular strain of the organism found and upon the patient s tolerance of the remedy If the organism proves unduly resistant to one antibiotic another should be substituted While penicillin is quite effective in a concentration of 1000 units per Gm against most of the organisms causing acute conjunctivitis, its continued use, especially in the ointment form leads to sensitization in a high percentage of cases and its use should probably therefore be restricted to those cases in which corneal complications are present or anticipated Sodium sulfacetamide as a 10 per cent ointment or 30 per cent solution is particularly useful Sulfathiazole or sulfadiazine 5 per cent bacitracin ointment (500 units per Gm), or aureomycin solution (25 mg in 5 cc, prepared fresh every two days) may be substituted if desired or indicated by bacteriologic study or clinical evidence of resistance to the remedy employed Of the more recently developed agents chloramphenicol 25 mg in 5–15 cc of isotonic sodium chloride, has proved to be one of the most effective therapeutic agents in the treatment of most forms of acute conjunctivitis

The ointment or solution employed should be instilled into the conjunctival sac every two or three hours during the waking hours, one or two drops of the solution or an equivalent amount of the ointment being used Local use of the antibiotics usually is adequate, there being no need for parenteral injection Additional local treatment may include irrigation of the eyes as necessary to remove secretion and the occasional application of 1 per cent silver nitrate solution to the everted conjunctiva The patient should be warned that the condition is infectious and to

* See also Chapter 40

after the infection has disappeared If this is not successful the sac should be extirpated or a dacryocystorhinostomy performed

STENOSIS

Closing of the nasolacrimal duct occurs not infrequently because of the persistence of a congenital membrane which has failed to disappear developmentally This type of stenosis, which is associated with the formation of tears and a mucopurulent secretion from the sac, can be treated with digital expression of the sac Pressure begins at the punctum and continues toward the nose in a downward direction Such treatment frequently will cause rupture of the membrane by hydrostatic pressure If this is not successful after a number of attempts the duct may be probed with the patient under a general anesthetic One probing is usually successful In the adult with stenosis probing should be undertaken under local anesthetic but this usually requires repeated stretching of the duct Eventually surgery may be required Inadequate drainage of tears may also be due to faulty position of the lid, as in ectropion and may require surgical correction

DACRYOADENITIS

This may occur spontaneously or as an accompaniment to mumps or other diseases Hot compresses are usually adequate as treatment, and incision is rarely necessary Other enlargements of the lacrimal glands such as occur in Mikulicz s disease, tuberculosis and Boeck s sarcoid do not require local treatment

HYPOFUNCTION OF THE LACRIMAL GLAND

The lacrimal gland may not function properly and may cause serious changes in the conjunctiva and cornea because of failure to provide moisture The treatment will be discussed under 'Keratitis Sicca The Schirmer test is used to determine the adequacy of tear formation Strips of filter paper (Whatman No 41 has been recommended) 35 mm × 5 mm are folded 5 mm. from the end and this fold is tucked into the lower cul de sac behind and in the outer third of the lid The number of millimeters of the filter paper not in the sac which become moist is measured after five minutes Normally the paper should be entirely moistened in that time Less than 15 mm should cause suspicion of hyposecretion If no tears are present the paper is, of course, quite dry Obviously no drops should be instilled in the eye prior to the test

Diseases of the Cornea

FOREIGN BODY

While the actual removal of a foreign body from the cornea is a surgical procedure which is not properly within the scope of this chapter, there arises frequently a question concerning what medication should be employed subsequent to the removal of the body Atropine should never be used but 2 per cent homatropine (1 drop) may be instilled if there is evidence of iris irritation and ciliary spasm (small pupil) A small amount of an ointment containing penicillin, sodium sulfacetamide, sulfathiazole, or other antibiotic may be instilled following which the eye usually is bandaged The patient should be seen the following day and examined for signs of infection which is evident if infiltration is present and the epithelium is not healing Early infection usually can be arrested by

tions being made twice weekly) if local treatment is not effective More rarely infections with other bacteria, such as the pneumococcus may result in a chronic conjunctivitis, but these usually respond well to local antibiotic therapy

ALLERGIC CONJUNCTIVITIS

This condition usually is associated with a blepharitis and its treatment is the same as that previously discussed in the section on blepharitis It is to be noted that continuous use of certain drugs especially penicillin, atropine, and eserine, as well as most local anesthetics, is a frequent cause of this condition, which disappears in a few days after discontinuance of the drug Local use of cortisone is highly effective in relieving the acute symptoms Its use is discussed under Allergic Blepharitis

NONSPECIFIC CONJUNCTIVITIS

This type of chronic conjunctivitis is by no means rare and is not always readily cured It may follow exposure to wind, water, dust, smoke or other irritants or may occur as an accompaniment of eyestrain An astringent solution such as 0 125 per cent zinc sulphate in 1 100 000 epinephrine solution frequently is of considerable help but it may be necessary to correct a refractive error, wear protective goggles in swimming (especially in highly chlorinated water), and avoid other mechanical irritants to control the condition satisfactorily

VERNAL CONJUNCTIVITIS

This is also known as spring catarrh, and lasts during the warm weather, recurring each spring It is characterized by extreme itching, cobblestone like plaques in the tarsal conjunctiva, or involvement near the limbus, with eosinophiles in the conjunctival scraping It can be treated only symptomatically as the exact cause is unknown Relief is usually afforded by the frequent instillations of a 1 4000 epinephrine solution to which procaine may be added to make a 1 per cent solution Some success has been obtained by using beta irradiation locally, and relief may be obtained by the local use of cortisone (6 mg per cc) Roentgen therapy or radium therapy should be used cautiously if at all, and only by those trained in its use

PEMPHIGUS

Pemphigus of the conjunctiva, although rare is an extremely serious disease, which results in blindness and disfigurement due to corneal complications and symblepharon Treatment is largely symptomatic and in later stages surgical Cortisone solution used locally in the conjunctival sac has recently been reported to have a favorable effect but the condition is so uncommon that no large series has as yet been studied

Diseases of the Lacrimal Apparatus

ACUTE DACRYOCYSTITIS

This infection of the lacrimal sac should be treated with parenteral administration of sulfonamides or penicillin, sufficient to maintain a blood level of 6-8 mg per 100 cc., hot moist compresses over the sac and incision into the sac to permit evacuation of the pus

CHRONIC DACRYOCYSTITIS

Chronic dacryocystitis may result from recurrent acute infection or from stenosis of the nasolacrimal duct It may be cured sometimes by repeatedly injecting penicillin ointment into the sac *through the* punctum by means of a lacrimal syringe If the duct is occluded it may be probed

SCLEROSING KERATITIS

This is usually regarded as tuberculous and desensitization with tuberculin may be of value Locally applied atropine may be necessary

SUPERFICIAL PUNCTATE KERATITIS

This condition is frequently extremely *resistant to treatment.* If heat and 3 to 5 per cent dionin solution have no effect one may try 2 per cent potassium iodide with 2 drops of compound iodine solution to the ounce (Cowan s solution) instilled in the eye three or four times daily Since many of these cases may be due to a virus, aureomycin (25 mg per 5 cc) or chloramphenicol (50 mg per 20 cc) may be tried locally every one or two hours Roentgen therapy may be effective but it should be used only as a last resort

KERATITIS SICCA

Keratitis sicca is caused by lacrimal gland deficiency, which may be demonstrated by the Schirmer test (see Hypofunction of the Lacrimal Gland) It requires the use of artificial tears or in severe chronic cases closure of the puncta The best substitute for tears is gelatin and chloretone' (120 mg of each in 30 cc of Locke s solution) or methyl cellulose (0 75 per cent solution) used as frequently as necessary (usually every hour) Strong medication or astringents make the condition worse and should be avoided

KERATITIS EILAGOPHTHALMOS

Occurring as a result of facial paralysis or severe exophthalmos, this condition may require the use of a moist chamber, which can be made by cutting, fitting and sealing with adhesive a piece of roentgen ray film to fully protect the globe Extreme cases may require the creation of adhesions between the upper and lower lids by surgery or, in the cases of exophthalmos removal of the roof of the orbit

KERATITIS NEUROPARALYTICA

Treatment must be undertaken with care because of the corneal anesthesia and the tendency for trophic disturbance The eye should be irrigated daily with isotonic solution of sodium chloride and a moist chamber employed if keratitis is present

INTERSTITIAL KERATITIS

Interstitial keratitis requires the use of atropine 1 per cent several times a day as there is always an accompanying uveitis but general treatment of the syphilis should be undertaken promptly * Induced fever therapy accompanying the antiluetic therapy may be of considerable help in hastening the healing of a rather protracted condition Following the active stage dionin 3 to 5 per cent solution four times a day may be of help in lessening the corneal scar

* See Chapter 39

Diseases of the Uvea

IRIDOCYCLITIS

Usually seen in an acute form iridocyclitis presents a difficult problem as formation of adhesions between the iris and the lens and obstruction of the pupillary portion of the lens by exudate (occlusio pupillae) may result in permanent impairment of vision It is extremely important therefore to secure prompt dilatation of the pupil and to maintain this during the

carefully applying trichloroacetic acid with a fine tipped applicator to the damaged area Supportive antibiotic therapy also is helpful In this way the development of a more severe corneal ulcer is prevented It is not advisable to prescribe anesthetics after foreign body removal in corneal diseases as epithelium repair may be delayed

SERPIGINOUS ULCER

The most severe type of corneal ulcer apart from that which complicates gonococcal conjunctivitis is the so called serpiginous ulcer usually caused by the pneumococcus This spreads rapidly and requires energetic treatment Trichloroacetic acid may be applied directly to the ulcer with a fine applicator or this may be varied by applying a thick syrup of iodine (made by mixing 5 drops of tincture of iodine, 5 drops of glycerine 600 mg of iodine crystals and 1 drop of saturated potassium iodide) This should be applied carefully to the ulcerated area the normal cornea being avoided Daily application may be made and if response is not rapid light application of a cautery or thermophore may be tried Heat by infrared lamp or hot moist compresses is indicated Frequent (hourly) instillations of penicillin or other antibiotics often are extremely helpful and most ulcers will respond under this type of therapy The pupil must be kept dilated with atropine If in spite of treatment the ulcer continues to progress it may be necessary to perform a paracentesis or delimiting keratotomy

MARGINAL ULCER

Marginal or catarrhal ulcer occurring chiefly in elderly or debilitated individuals is usually cured by the application of trichloracetic acid to the ulcers and by local antibiotic therapy, but it frequently tends to recur and may require systemic treatment for an anemia or vitamin deficiency which may be present

RODENT (MOOREN S) ULCER

This is resistant to all medication but may be helped by a keratotomy (kept open daily for several weeks) or by a sliding conjunctival flap

DENDRITIC KERATITIS

Dendritic keratitis, or herpes simplex of the cornea is best treated by applying syrup of iodine to the ulcer as described under Serpiginous Ulcer, the applications being made daily or on alternate days to all of the area which can be stained with fluorescein Aureomycin or terramycin solution (25 mg per 5 cc) or chloramphenicol (50 mg per 20 cc) should be instilled once an hour in the conjunctival sac, with aureomycin ointment at bedtime Frequently this will have a marked beneficial effect Other antibiotics are useful only to combat secondary infection Atropine is instilled daily Refractory cases may be treated with light roentgen ray therapy one third of an erythema dose being employed

PHLYCTENULAR KERATOCONJUNCTIVITIS

This disease requires the local use of atropine (1 per cent solution two or three times a day) and some stimulating substance such as yellow oxide of mercury ointment calomel or 3 per cent dionin solution applied at home three or four times a day Most important is, however, the general treatment which requires adequate diet rest Vitamins A and D, sunlight and possibly calcium Thorough search should be made for active tuberculosis and in some selected cases careful desensitization with tuberculin may be attempted Local cortisone drops are often helpful

It is important that patients on this therapy receive adequate laboratory studies to avoid untoward effects especially on the glandular system and electrolytic balance The use of cortone (cortisone acetate) drops locally instilled into the conjunctival sac has proved to be as efficacious in the treatment of iritis as has the parenteral use and it has the advantage of simplicity economy, and complete freedom from side effects While it is usually employed in a 1 4 dilution it may be used up to full strength (25 mg per cc) with only a moderate burning sensation produced by the benzyl alcohol used as a preservative The drops should be instilled every one or two hours

Increased intraocular tension occurring during the course of iridocyclitis should be treated by paracentesis reopening the incision daily if necessary Atropine must be continued in spite of the tension The practice of alternating the mydriatic with a miotic is not recommended

CHOROIDITIS

Choroiditis is similar in etiology to iridocyclitis and is treated in the same way except that the anterior segment is not involved and there is not the same urgent necessity of keeping the pupil dilated This disease requires a thorough search for and removal of the cause and the use of salicylates and foreign protein when the condition is acute The local use of cortisone is less effective than in anterior uveitis but in many cases parenteral use of cortisone or ACTH may cause the acute inflammatory process in the choroid and retina to subside As in all forms of uveitis the diagnostic acumen of the clinician is challenged in determining the etiology Some cases are due to an allergic response to tuberculin although active tuberculosis may not be demonstrable clinically If the Mantoux intradermal test with tuberculin* is positive and all other findings negative one may carry out a desensitization with tuberculin One must bear in mind the possibility of allergy and intestinal foci as well as the more commonly recognized sources of infection if treatment is to be adequate Otherwise if permitted to continue and recur, it may become a most disabling condition

SYMPATHETIC OPHTHALMIA

This occurs as a result of involvement of a healthy eye following a penetrating injury to the other eye and is a serious form of uveitis which may lead to bilateral blindness The most important part of the treatment is prophylactic Any eye with a penetrating wound which develops a chronic uveitis and which does not heal should be enucleated Injuries in the region of the ciliary body are particularly apt to produce this condition Sympathetic ophthalmia is a clinical entity which can be diagnosed with certainty only by examination of the uveal tract of the enucleated eye However the diagnosis may at times have to be made solely on clinical signs and the condition treated energetically Atropine applied locally large doses of salicylates (30 mg per day per kg body weight) and foreign protein injections should be employed If early treatment is instituted cortisone locally or ACTH or cortisone parenterally and cortisone locally may be of help If the second eye has only begun to show evidence of irritation the injured eye should at once be removed but if the condition is well developed in the other eye it is too late to save the eye and enucleation should perhaps not be done

* See Chapter 19

entire course of the disease, which usually is from three to six weeks In early cases the instillation of 1 per cent solution or oint ment of atropine sulfate four times a day may be sufficient If adhesions are already present and the pupil does not dilate fully in a few hours additional mydriatics should be employed Two or three drops of 'neo synephrine hydrochloride 10 per cent (solution or emulsion), or 1 100 epineph rine solution may be instilled in the eye after it has been anesthetized with two drops of butyn, holocaine, or other local anesthetic An alternate method is the sub conjunctival injection of a mixture of two drops each of 2 per cent atropine 2 per cent cocaine, and 1 1000 epinephrine When the pupil is well dilated and ad hesions have been broken continued use of atropine will usually be sufficient to keep the pupil dilated but the other my driatics may be employed again if necessary Should an atropine reaction occur after prolonged use of scopolamine hydrobro mide 0 2 per cent may be substituted

Of importance in the treatment is the determination of the source of the infec tion, which may be syphilis tuberculosis brucellosis sarcoid toxoplasmosis histo plasmosis, lymphogranuloma venereum leprosy, or a focus of infection occurring in the teeth sinuses tonsils prostate or fallopian tubes and more rarely the gall bladder or appendix If the eye infection is not too severe general or surgical treatment of the cause should be undertaken imme diately In some instances it may be well to wait until the most acute stage has passed before undertaking surgical procedures such as tonsillectomy If the cause is not found the patient will recover from the attack but is almost certain to have a re currence

The use of salicylates on a purely empiric basis has long been of help in the treatment of iridocyclitis Adequate dosage usually 5–7 Gm per day, of sodium sali cylate should be administered orally The concurrent administration of a similar amount of sodium bicarbonate followed by copious amounts of water will reduce gastric irritation from the salicylates Antibiotics have not proved helpful and are not ad vised unless for the treatment of a demon strated infection believed to have an etiologic relationship Foreign protein should be given in the more severe cases, usually in the form of triple typhoid vac cine administered intravenously As a rule adequate effects are obtained with the smaller dosages Treatment, beginning with 10 or 20 million killed organisms, is in creased each injection by 5 or 10 million depending upon the reaction obtained which is usually judged by the subjective symptoms of chills general discomfort, and rise in body temperature Patients should be hospitalized for this treatment and it should not be forgotten that incautious use of foreign protein may result in ex treme hyperpyrexia and death Salicylates should be temporarily discontinued during the administration of foreign protein

Adrenocorticotropic hormone (ACTH) and cortisone have recently been used rather widely in the treatment of all forms of uveitis except when an active tuberculosis is present They are not uniformly spec tacular in promoting an immediate cure but in many cases there is a dramatic re sponse, shown by alleviation of the more acute subjective and objective symptoms and shortening of the course of the disease Their parenteral use should probably be limited to the most resistant cases especially the iritis seen in conjunction with rheuma toid arthritis

Cortisone is administered intramuscu larly 100 mg every eight hours for the first day, then 100 mg every twelve hours the second day and 100 mg per day thereafter ACTH is usually used in doses of from 50 to 100 mg per day in divided doses, decreasing after the first few days

is the necessity for continued therapy and *careful supervision* An operation should be performed as soon as medical treatment becomes ineffective

General treatment is important Coffee and tea are to be avoided and the patient should avoid fatigue excitement, and worry

ACUTE GLAUCOMA

Acute glaucoma of the congestive narrow angle type, requires energetic treatment with surgical intervention (usually an iridectomy) if medical measures do not reduce the intraocular tension in twenty four hours Escrine 1 or 2 per cent is instilled at hourly intervals or a mixture of 2 per cent pilocarpine and 0 2 per cent eserine is administered in an eye cup (the only indication for the use of this object) *to permit frequent conjunctival baths* Morphine 5 to 7 mg will be helpful in controlling the intense pain causing the patient to relax to produce miosis Cold applications to the eye will assist in reducing the congestion and edema Saline purges may be prescribed Intravenous injections of *hypertonic sodium chloride* (50 cc of 30 per cent sodium chloride) or glucose 100 cc of a 50 per cent solution may be given One of the best solutions for intravenous injection is 100 cc of 50 per cent sorbitol solution which frequently will reduce the tension promptly

If glaucoma is secondary to some other condition it is important that this be recognized and the underlying cause treated Thus in ocular hypertension secondary to iritis miotics must be avoided the iritis being treated and the tension controlled if necessary with a paracentesis If the disease *is due to a dislocated lens the lens must be* removed and if it is due to an intraocular tumor the eye will have to be enucleated One must avoid treating the symptoms without determining the source of the glaucoma if this is possible

Diseases of the Retina

OCCLUSION OF THE CENTRAL RETINAL ARTERY

Occlusion of this artery or one of its *branches occurs with sudden loss of vision* and requires prompt treatment if treatment is to be effective An immediate paracentesis should be performed the globe *massaged* and vasodilators employed Amyl nitrite by inhalation may be used first followed by nitroglycerin 3 mg administered subcutaneously and sodium nitrite 30 mg three times a day orally for several days *Dicumarol therapy* may be employed if facilities are available for its proper control * General treatment of the vascular system should be employed to avoid occlu*sion of other vessels especially the artery* of the other eye

THROMBOSIS OF THE CENTRAL RETINAL VEIN

This also occurs suddenly The only treatment which has been proved effective is early use of anticoagulants such as heparin or dicumarol These should be used only if the patient is controlled adequately General examination *of the cardiovascular* system is important If treatment is indicated it should be given It is frequently wise to employ weak solutions of pilocarpine (0 5 per cent) because of the tendency *for secondary glaucoma to occur*

* See Chapter 13

Diseases of the Lens

CATARACT

Cataract, or opacity of the lens, is the only important disease of the lens The only cure for lens opacity is surgical removal of the cataract and this is indicated when the lens has become completely opaque or when the visual acuity in the better eye has been sufficiently reduced that the patient is no longer able to read and perform his usual occupations

The ordinary senile cataract has been treated with many forms of therapy including potassium iodide dionin, and vitamins, but there is no satisfactory evidence that they are effective Medical treatment aside from that intended to maintain the individual in the best possible health is probably not advisable Glasses should be prescribed to improve the vision but they may require changing frequently because of advancing lens sclerosis ('second sight) which causes increasing myopia In describing the early stages of cataract, which is present in most senile individuals, the word cataract should be avoided as, to the patient, this may be synonymous with ' blindness whereas actually the opacities may never develop this far

In the presence of diabetes control of the disease is important as this alone may halt further increase in the lens opacities Cataract due to parathyroid deficiency may respond to the use of parathyroid extract and calcium This treatment may be helpful in preventing further opacities but will not result in disappearance of lens opacities already present

Glaucoma

CHRONIC GLAUCOMA

Chronic noncongestive glaucoma is an insidious condition with few subjective symptoms to diagnose it so that one must be constantly on the alert Since treatment will do no more than prevent further loss of central vision and visual fields early diagnosis is extremely important Medical *treatment should always be attempted first* surgical intervention being undertaken only if the intraocular tension is not controlled and the visual fields show increasing loss Pilocarpine 0 5–1 per cent four times a day should be prescribed first and continued as long as the glaucoma is controlled If this becomes ineffective the concentration may be increased to 2–3 per cent and if in turn this loses its efficacy eserine salicylate 0 2 per cent solution or 0 25 per cent ointment may be substituted If eserine must be used to control the tension it is quite likely that in time it too will no longer be effective Various new miotics have been introduced and may be tried before surgery (which involves a ' filtering operation) is advised Included are *3 per cent prostigmine with 10 per cent* mecholyl," "doryl ' 0 75 to 1 5 per cent solution, and di isopropyl fluorophosphate (DFP) 0 05 per cent solution in peanut oil The latter drug is the most potent and is the longest acting miotic now known It may be used only twice a day or once in several days It is most effective in aphakic glaucoma To be emphasized in the treatment of this type of wide angle glaucoma

scotoma without ophthalmoscopic evidence of pathology until the stage of atrophy occurs The most frequent form is known as alcohol tobacco amblyopia Of paramount importance *in treatment is the im*mediate withdrawal of both of these substances Since this condition is to a large extent a problem associated with dietary insufficiency an adequate diet should be prescribed, this being supplemented with thiamine chloride, 50 mg per day intravenously for several days followed by 20 mg per day by mouth or large doses of vitamin *B* complex Vasodilators (sodium nitrite or nitroglycerine by mouth) may also be helpful Other causes of toxic amblyopia include severe hemorrhage, avitaminosis, *pregnancy,* and lactation, and aniline and carbon monoxide poisoning each of which must be treated specifically where possible *

PAPILLEDEMA

The only treatment is removal of the cause which is usually increased intracranial pressure If allowed to continue it eventually will cause secondary atrophy and blindness

* See Chapter 50

OPTIC ATROPHY

This is an irreversible condition which cannot be alleviated by any treatment Therapy can only prevent further progress That which is due to cerebrospinal syphilis cannot be treated with antisyphilitic therapy alone, as it is of no value, furthermore, pentavalent arsenic particularly should be avoided However, hyperthermia combined with antisyphilitic treatment is of value in some cases and may be tried A fever cabinet in which a temperature of 105° F is induced for several hours probably is the *most reliable method of this form of ther*apy, although it is not free of marked discomfort and some danger * Other methods of treatment such as intracisternal in*jections of mercuric chloride (0 1 mg)* are also not free of danger, such as causing death or brain damage

* See Chapter 39

Diseases of the Orbit

ORBITAL CELLULITIS

Orbital cellulitis requires an examination to determine whether the source of infection is in the paranasal sinuses, is a bacteremia, or *stems from erysipelas or* facial furunculosis Treatment is then directed towards the cause but the local use of heat (infrared lamp or moist heat) should be instituted Penicillin therapy in large doses will frequently abort the condition if it is given early If free pus is present and the infection points it should be incised and drained, penicillin therapy being continued *Sulfonamides may* be substituted or given in conjunction with penicillin

CAVERNOUS SINUS THROMBOSIS

This is a serious condition and should be treated with large doses of penicillin Anticoagulant therapy in combination with antibiotics may be tried

EXOPHTHALMOS

This condition must be carefully investigated Studies of the basal metabolism roentgen ray examination of the or*bit and* laboratory tests will aid in determining the cause A malignant form may occur after thyroidectomy, it is believed to be due to disturbance in the activity of the pituitary gland It may be relieved by the use of thyroid extract if use of this drug is

CENTRAL ANGIOSPASTIC RETINOPATHY

This condition requires an examination of the patient's peripheral vascular system especially his response to tobacco which is a frequent cause of the disease Treatment includes besides the elimination of tobacco the use of antispasmodics the intravenous administration of typhoid vaccine during the acute phase barbiturates rest, and other measures to produce relaxation

PERIPHLEBITIS RETINAE

Associated with recurrent vitreous and retinal hemorrhages, this condition is usually of tuberculous origin and treatment must be directed towards obtaining rest adequate diet and sunlight * Tuberculin therapy may be employed in selected cases, but great care must be exercised in its use It may be begun with minute doses (approximately 0001 mg of old tuberculin) Rutin therapy 120 mg per day for a prolonged period, may be tried, although its value in this type of case is open to question

* See Chapter 16

DIABETIC RETINOPATHY

As a complication of diabetes mellitus, this condition requires treating the patient by controlling the diabetes,* although the retinal condition may progress in spite of complete control because of the vascular involvement Rutin 120 mg per day, and saturated solution of potassium iodide, 5 drops three times a day may be employed but the results frequently are disappointing

ARTERIOSCLEROTIC AND HYPERTENSIVE RETINOPATHY

Neither condition is affected favorably by local or general treatment except by that which may be indicated for the causative condition e g, sympathectomy or drugs to control hypertension

* See Chapter 31

Diseases of the Optic Nerve and Central Visual Pathways

OPTIC NEURITIS AND RETROBULBAR NEURITIS

These inflammatory lesions require a complete examination if the cause is to be determined so that appropriate specific treatment may be instituted The commonest cause of an optic neuritis ophthalmoscopically visible is syphilis whereas multiple sclerosis is the most frequent cause of the retrobulbar variety Only nonspecific therapy can be employed when the cause cannot be discovered and when multiple sclerosis is believed to be the cause This includes the use of nonspecific protein therapy (typhoid vaccine) vasodilators (such as 1 cc of sodium nitrite 10 per cent solution intravenously daily) and vitamin B complex or thiamine chloride (20 to 50 mg daily by intravenous or intramuscular route) If the cause is poisoning by lead, methyl alcohol quinine, digitalis, or thallium the responsible agent should be removed promptly* and the preceding treatment initiated Syphilis requires prompt treatment Sinus infection requires adequate drainage of the paranasal sinuses If a tryparsenamide reaction occurs 10 cc of 10 per cent solution of sodium thiosulfate may be administered intravenously daily for several days

TOXIC AMBLYOPIA

This form of an intoxication may be difficult to distinguish clinically from retrobulbar neuritis as both cause a central

* See Chapter 50

an application of trichloroacetic acid and a binocular pressure dressing for several days

CONTUSIONS OF THE EYEBALL

This may give rise to traumatic cyclitis (requiring use of atropine) and retinal edema Since the latter condition may cause retinal detachment eyes with such injuries must be kept at rest with a binocular dressing for several days following which strenuous exercise is forbidden for some weeks If hemorrhage occurs in the eye as a result of the contusion watch must be kept for secondary increase in intraocular tension Such hemorrhages are usually absorbed but extensive hemorrhage in the anterior chamber with secondary rise in tension may require a keratotomy with irrigation to remove the clotted blood

permissible Irradiation of the pituitary may be tried and is sometimes successful If the condition is associated with hyper thyroidism thyroidectomy may be the treatment of choice It may be necessary to protect the cornea by use of a transparent moist chamber or by suturing the lids together In extreme cases removal of the roof of the orbit may have to be carried out (Naffsiger s operation) if the eyes are to be preserved for useful vision

Injuries and Emergency Treatment

THE removal of foreign bodies from the cornea has been discussed under Cornea Foreign bodies loose in the conjunctival sac ordinarily require nothing more than gentle removal with a moist applicator or clean piece of lintless cloth Intraocular foreign bodies and lacerations of the globe and lids require prompt surgical intervention not within the scope of this chapter There are however, emergency treatments which must be given for other types of injuries and which must be instituted as promptly as possible to avoid serious damage to the ocular tissues

CHEMICAL BURNS

Chemical burns of the eye should be treated immediately with any nonirritating solution to permit thorough irrigation of the eye and removal of all of the chemical which has not already combined with the tissues Tap water is the most convenient thing although if at hand isotonic solution of sodium chloride or saturated boric acid solution are less irritating to the ocular membranes Neutralization of an acid or alkali is ordinarily not necessary and may do harm if an excessively strong solution is used If an attempt is made to neutralize an acid 3 per cent sodium bicarbonate solution may be used (no stronger) For alkalis 1 per cent acetic acid solution is useful Dimercaprol ("BAL") has been successfully used to neutralize Lewisite, but generally speaking one should be content to irrigate the eye thoroughly twice as long as is thought necessary with ordinary tap water Lime burns may be treated with freshly prepared 5 or 10 per cent solution of neutral ammonium tartrate, instilled several times a day for several days Lime burns are particularly severe and may require a mucous membrane or other type of graft Tear gas burns may be treated with 0 4 per cent solution of sodium sulfite in water and glycerine

The cornea should be examined after all chemical or thermal injuries to determine the extent of damage A drop of fluorescein is instilled and the excess washed away, this will show the extent of damage to the corneal epithelium Too extensive use of local anesthetics to relieve pain is inadvisable but an antibiotic ointment or sodium sulfacetamide 30 per cent solution may be instilled and a pressure dressing applied, the eye being examined after twenty four hours at which time the epithelium frequently will be found to be healed if no infection has occurred in the tissues of the cornea

CORNEAL EROSIONS

These may occur and recur many times in the scar left from certain types of corneal infection following injuries, especially those produced by the human fingernail They may require removal of a considerable amount of corneal epithelium followed by

Roentgen Ray Treatment

Therapy with roentgen rays, which inhibit activity of the sebaceous glands, is the most effective method It is safe in the hands of well trained dermatologists However, along with roentgen ray therapy, other effective measures should be employed Roentgen rays in doses of 75–100 r per week for a total of eight to twelve treatments usually suffice The voltage varies from 60 to 100 Kv and the half value layer should be 0 5–1 0 mm of Al This treatment should be administered only by a physician who is familiar with the natural history of the disease and with the general principles of roentgen therapy Because many cases of acne respond to more simple methods of treatment and because the routine use of roentgen rays may produce undesirable sequelae in some patients it is advised that this form of therapy be held in abeyance until other effective methods have been given a thorough trial

Local Treatment

Local treatment requires washing the face twice a day with soap and water oily preparations should be avoided The patient should not traumatize the face by attempting to remove comedones and evacuate pustules but should leave their removal to the physician who can provide treatment without damaging normal surrounding skin *Exfoliating and antiseptic* agents to rid the skin of lipid deposits (comedones) and to dry up pustules are commonly employed The patient can be instructed to use each night the following lotio alba whose strength can be gradually increased by the addition of increased quantities of active agents (up to 12 per cent) and resorcin (up to 5 per cent)

	Gm or cc
Zinc sulfate	4
Sulfurated potash	4
Rose water to make	120

If still stronger treatment is required Vleminckx's lotion may be used

	Gm or cc
Lime	15
Sublimed sulfur	30
Distilled water to make	300
Mix and boil down to 180 cc and filter	

Ultraviolet Light

Exfoliation with ultraviolet light using either the hot or cold quartz apparatus or natural sun is beneficial The dosage depends upon the sensitivity of the skin to ultraviolet light, and the type and condition of the ultraviolet ray lamp In general mildly erythematous doses of ultraviolet light are administered once or twice a week or even daily in severe cases The treatment is administered for several months Peeling of the skin may be done with strong topical preparations but this is not advisable because it may be dangerous and the results at best are only temporary

Solid Carbon Dioxide

Solid carbon dioxide which has been pulverized and to which are added pulverized precipitated sulfur in the proportions of 1 part of sulfur to 8 parts of pulverized solid carbon dioxide and enough acetone to convert the powdery mixture to a slushy state, has been used Some acne cases are benefited by this method of treatment It also is helpful in minimizing superficial scarring resulting from active lesions of acne vulgaris

Surgery

Acne surgery which includes the removal of comedones and the evacuation of pustules at regular intervals is definitely beneficial when done properly by the physician Unnecessary roughness and trauma in treating comedones and pustules may cause greater scarring

The scalp should be kept scrupulously clean even though daily washing is re

38. Dermatologic Diseases

ANTHONY C CIPOLLARO
& ADRIAN BRODEY

THE following diseases were selected because they are commonly encountered and lend themselves to therapeutic discussion Some dermatologists might have added others and other dermatologists might have deleted some we selected An attempt has been made to include diseases most commonly encountered in office and clinic practice

We have purposely omitted detailed and involved management of some diseases because such treatment should be administered by a specialist or under his supervision The emphasis in the treatment section of each disease has been on practicability and availability For example the treatment of acne vulgaris with roentgen rays is a highly technical procedure requiring detailed knowledge of the disease and of the use of roentgen rays A well trained dermatologist has this information but a well trained internist does not nor does a well trained roentgenologist The same logic applies to the treatment of tinea capitis with roentgen rays However for use by the general practitioner we have given those methods of treatment which are available to him and which should be effectual in the majority of cases

The Pyogenic Group

ACNE VULGARIS

The general practitioner probably encounters more cases of acne vulgaris than any other skin disease and yet successful therapeutic results are rare Perhaps it is because the importance of acne is often unrecognized It occurs during adolescence when the patient is developing psychologically as well as physically There is a tendency for the sufferer to avoid social life and even to avoid contact with all but a few intimate friends There may be a sense of humiliation inferiority and discouragement Such patients are apt to become reticent introspective morose irritable and exceedingly sensitive Thus in addition to specific acne therapy patients suffering from acne require psychologic treatment

tion and gonadal disturbances are corrected and measures should be taken to improve the general health Telangiectases are de stroyed with electrolysis Roentgen rays and ultraviolet light are not particularly efficacious Small doses occasionally help some cases They should not be used rou tinely

IMPETIGO CONTAGIOSA

The sulfonamides and penicillin locally applied will quickly cure a patient of im petigo contagiosa However, these agents are strong sensitizers and it is best to avoid them if possible Neomycin, polysporon tyrothricin, bacitracin aureomycin and terramycin in ointment form are valuable agents are less sensitizing and are just as efficacious as the other remedies They can be used also in solution The use of 2 to 10 per cent ammoniated mercury still is one of the best remedies for impetigo contagiosa and is inexpensive and easily obtainable Many patients fail to recover promptly because the crusts are not removed before application of the ointment and because soap and water are not used freely

Many cases will heal more promptly if individual lesions are painted with 2 per cent gentian violet, 5 per cent silver nitrate or 3 per cent copper sulfate Suberythema doses of ultraviolet rays are sometimes valu able in stubborn cases but must be used concurrently with topical applications of medicinal agents Parenteral penicillin or an antibiotic by mouth are valuable in extreme and recalcitrant cases

NEONATAL IMPETIGO

Pemphigus neonatorum is seen less fre quently than formerly and the fatalities from this disease have decreased markedly There are various ways of preventing im petigo of the newborn One is to avoid bathing the newborn baby, another is to anoint the entire body after birth with 2 per cent ammoniated mercury ointment The personnel of the delivery room and in the nursery should be absolutely free of staphylococcic infections and the linens touching the baby must be sterile

Injections of penicillin and the admin istration of a broad spectrum antibiotic or a sulfonamide should be undertaken when the infection is extensive In mild cases preparations containing ammoniated mer cury, tyrothricin, bacitracin, aureomycin terramycin, or neomycin can be applied locally Opening the blisters and painting the surface with mild aqueous solutions of gentian violet, silver nitrate, or copper sul fate are valuable In more extensive cases bathing in a 1 10 000 solution of potassium permanganate is efficacious

ECTHYMA

Ecthyma is thought by some to be an ulcerative variety of impetigo contagiosa It occurs mostly in children and involves usually the lower extremities of individuals who are in poor health or whose hygienic habits are bad

The treatment is similar to that of im petigo contagiosa but in addition it is necessary to build up the patient s general health Frequent use of soap and water and cleansing baths cannot be emphasized too strongly Some of the deeper ulcerative lesions may be cured with wet dressings of potassium permanganate (1 5000) or solutions of bacitracin or tyrothricin dur ing the day, and with one of the antiseptic ointments such as neomycin, ammoniated mercury, tyrothricin, bacitracin or aureo mycin during the night

FURUNCULOSIS

The ordinary single furuncle is easily treated by incision and drainage While the furuncle is developing continuous hot applications of a 2 per cent boric acid solu tion or a 10 per cent magnesium sulfate solution will minimize pain and hasten

quired In some patients 5–10 per cent sulfur or ammoniated mercury ointment is required For the more severe cases, 2 per cent salicylic acid should be added to these ointments Local treatment alone will not control many cases of acne, it is necessary also to employ general treatment

General Treatment

General treatment requires attention to the general health of the acne patient as it is of the utmost importance There should be daily evacuations foci of infection must be removed diet, rest and exercise should be prescribed according to individual requirements and secondary anemia should be corrected Occasionally acne is associated with a food allergy Some drugs such as bromides and iodides will cause an acneform eruption, and these should be interdicted in all cases of acne The antibiotics and the sulfonamides are helpful in those cases in which there are large infected cystic lesions, large pustules and small abscesses (acne conglobata)

Hormones The use of hormones for the treatment of acne is becoming more popular daily We question the wisdom of prescribing hormones in doses sufficient to cause physiologic changes such as tenderness of the nipples in adolescent children who according to chemical examinations and laboratory tests appear to possess normal hormonal functions When there is a definite hormone deficiency the administration of endocrines may favorably influence the course of acne vulgaris We are opposed to the routine use of hormones in any dose for the treatment of acne vulgaris in boys or girls who are otherwise normal

Diet Since acne is essentially a disturbance of lipid metabolism a diet restricting fats and the administration of thyroid helps many cases The correct dose of thyroid is found by trial but the usual starting dose is 60 mg taken with the breakfast The diet is liberal, permitting all the carbohydrates and proteins the patient can eat, but restricting the fatty foods, especially whole milk, cream, butter, ice cream, cheese, gravy, salad dressings, ham pork, fried foods, chocolate, tomato juice, carrots, orange juice, and cod liver oil Dieting alone will not help acne vulgaris

The vitamins have been employed, especially vitamins A and D Vitamin A in doses of 50 000 units given once to three times a day has been beneficial in some stubborn cases of acne vulgaris Supportive treatment with crude liver extract in 2 unit doses twice a week or the use of vitamin B_{12} has also been efficacious

Vaccines and toxoids have been employed for years They are less popular today than they were even five years ago Very little is to be expected from the routine use of stock vaccines, toxoids, or bacteriophage

ACNE ROSACEA

Acne rosacea occurs on the nose and adjacent portions of the cheeks forehead, and chin and is characterized by redness, oiliness and acneform inflammatory lesions It occurs most commonly in women and is associated with gonadal disturbances infectious foci, constipation, and excessive indulgence in the use of alcohol and tea *Demodex folliculorum* is thought by some to be the causative organism Sometimes rosacea is associated with keratitis and conjunctivitis

Treatment

Patients with rosacea respond satisfactorily to treatment Alcohol tea, spices and fats are interdicted or restricted Many patients do well on small doses (5 drops) of dilute hydrochloric acid with each meal Locally the use of a mild preparation of white lotion is beneficial In some patients, the response to 40 per cent sulfur paste is gratifying

Infectious foci are removed Constipa

staphylococci It is usually associated with *poor general health and the presence* of a chronic infection of the upper respiratory tract The affection is chronic and obstinate and recurrences are common

Results are satisfactory when several methods of treatment are used conjointly Attention to general health and removal of foci of infection are essential The liberal use of soap and water is beneficial The general resistance is sometimes improved by vaccines, toxoids and liberal amounts of vitamins, especially vitamin A When the disease is extensive, penicillin by injection (*300,000 units daily*) or *sulfadiazine* (0 5 Gm three times a day) by mouth may be helpful Streptomycin and the broad spectrum antibiotics are useful

Many patients respond exceptionally well following the nightly application of an ointment containing 2 per cent salicylic acid and 6 per cent ammoniated mercury The following formula has proved to be the only remedy to cause involution of lesions in some instances

	Gm or cc
Oxyquinoline sulfate	0 25
Benzoyl peroxide	5 0
Eucalyptol	0 5
Thyme oil	0 5
Petrolatum to make	50

Three per cent 'vioform ointment, tyrothricin and *bacitracin in ointment or solution*, and aureomycin or terramycin ointment are also valuable agents

Roentgen ray therapy will sometimes succeed where all other methods have failed It is not advisable to administer more than eight weekly treatments of low voltage (100 Kv) unfiltered or lightly filtered (1–3 mm Al) in doses of 75–100 r Formerly it was *considered proper therapy* to give sufficient roentgen rays to cause permanent defluvium of the beard but this drastic method of treatment for sycosis vulgaris went out of favor twenty years ago We certainly do not advocate it because such treatment will eventually lead to radiodermatitis

GRANULOMA PYOGENICUM

Lesions of granuloma pyogenicum usually occur at the site of the trauma They occur as small red, globular, elastic nodules varying in size from a pinhead to a pea and may occur any place on the surface of the skin or the accessible mucous membranes Bleeding occurs on slight traumatization. Treatment consists of destroying the lesions with electrodesiccation under local procaine anesthesia

ERYSIPELAS

Erysipelas is no longer the dreaded disease of the very young and the very old that it was prior to the discovery of the sulfonamides, as it responds exceptionally well to moderate dosages of these drugs Sulfadiazine, 1 Gm every four hours for two or three days, followed by 0 5 Gm for several more days is usually sufficient for the ordinary case of erysipelas *More often* penicillin in oil is prescribed in doses of 300,000 units every day for five to seven days Aureomycin or terramycin, 0 25 Gm every six hours, is effective

Rest in bed good nursing care, the forcing of fluids, proper diet, and isolation of the patient are important For relief of local discomfort wet dressings of 2 per cent boric acid solution are *valuable Other* treatments, such as roentgen ray therapy the application of ultraviolet light and the use of antistreptococcus serum are obsolete Penicillin is probably the agent most often employed for the treatment of erysipelas

evolution The application of a single dose of 150 r of low voltage (100 Kv) lightly filtered (3mm Al) roentgen rays will have an anodyne effect and may abort the furuncle Rapidly spreading furuncles or those accompanied with cellulitis lymph angitis or lymphadenopathy and systemic symptoms require treatment with an anti biotic such as procaine penicillin in doses of 300 000 units or more per day until the lesion shows definite signs of involution Likewise lesions affecting the nose or upper lip should be treated with injections of penicillin or a broad spectrum antibiotic

Multiple recurrent furunculosis is usually associated with constant tension poor gen eral health chronic focus of infection, secondary anemia poor hygiene or para sitic infestations In some cases the cause is an unexplained lowered resistance to the staphylococcus The local treatment is somewhat similar to that described for the treatment of single lesions with the addi tion of daily exposure to ultraviolet rays and daily medicated baths

The best medicament for the bath is potassium permanganate The patient is usually instructed to dissolve *ten 5 grain* tablets in an average sized bath tub con taining forty to fifty gallons of hot water After bathing and treatment of the indi vidual lesions the remaining normal skin is sprinkled with a mildly antiseptic powder such as the following

	Gm or cc
Pulverated boric acid	12
Thymol iodide	6
Zinc stearate	24
Talc	120

Penicillin 300 000 unit doses daily for a total of 2 million units or the sulfonamides by mouth are valuable Aureomycin or terramycin in 0 25 Gm doses three to six times a day are also helpful in overcoming systemic infection Occasionally patients re spond well to an autogenous vaccine Of course, everything possible should be done to restore good general health and soap and water should be used generously

CARBUNCULOSIS

Carbuncles resemble furuncles except that they are larger, more painful and accompanied by systemic symptoms, and are frequently associated with diabetes Every individual with a carbuncle requires a general medical examination including tests on the urine and blood for signs of diabetes If there is elevation of temper ature, a blood culture should be made The ordinary small carbuncle can be treated as a boil, with incision and drainage when there is free pus surrounded by intact skin With the use of antibiotics especially peni cillin mutilating and painful operations are only seldom necessary Aureomycin and terramycin are as efficacious as penicillin While the carbuncle is in the stage of pain ful induration, one dose of 150 r of low voltage (100 Kv) unfiltered roentgen rays repeated in three days if necessary will have a pronounced anodyne effect

PARONYCHIA

Pyogenic paronychia may be acute or chronic and may involve one or more fingers or toes Continuous moist dressings of 10 per cent magnesium sulfate solution during the day and applications of tyro thricin ointment during the night are all that is usually necessary Some of the more recalcitrant infections may respond to bacitracin solution and ointment or to peni cillin, terramycin or aureomycin ointment Some cases may even require low voltage (100 Kv) unfiltered roentgen ray therapy in doses of 75 r per week for a total of four to eight treatments When there is localized accumulation of pus drainage must be established by a small incision or by re moval of a portion of the fingernail

SYCOSIS VULGARIS

Sycosis vulgaris is usually *limited to the* bearded area and is a folliculitis caused by

Prophylactic measures are important The dusting powder should be used daily before putting on shoes and after bathing It is impracticable to attempt to sterilize shoes However, shoes and hose should be changed daily

Dermatophytids *require soothing topical* medicaments such as compresses of 2 per cent boric acid solution and application of boric acid ointment or zinc paste and active treatment such as outlined above of the original focus

Roentgen rays in doses of 75 r per week for four weeks and ultraviolet radiation *may be appropriate in selected instances* of dermatophytosis which are recalcitrant to ordinary methods of treatment However it is seldom necessary to use roentgen rays for the treatment of dermatophytosis

ONYCHOMYCOSIS

Ringworm of the nails is a frequent source of reinfection in dermatophytosis The disease is difficult to cure and requires persistent effort

When only one or two nails are affected surgical evulsion of the nail followed by the use of fungicides may be considered However reinfection is common and the disability from the removal of several toe nails is severe Therefore more conservative measures are usually employed

Partial evulsion by the mechanical removal of infected nail tissue is accomplished by the use of scissors scraping with a scalpel fine emory board or glass slide This procedure is performed daily following *the application* of a 2 per cent aqueous solution of sodium hydroxide The nails are soaked for one half hour each day in hot *potassium permanganate solution* (1 6000) Full strength Whitfield s ointment is applied to the nails nightly and covered with *adhesive plaster The surrounding* skin must be protected with petrolatum from this strong medicament

For monilia infections of the nails daily painting with 2 per cent solution of gentian violet is often useful Roentgen ray therapy in weekly doses of 75 r hastens the involution of monilial paronychia and may be indicated in severe cases

Mild tincture of iodine 1-2 per cent iodine crystals in carbon tetrachloride or *1-10 per cent* chrysarobin in chloroform may be painted on the nails daily Ammoniacal silver nitrate has been recently advocated for the treatment of onychomycosis because of its fungicidal properties *and ability to penetrate keratin The results* have been poor

TINEA CAPITIS

Tinea of the scalp is rare after the age of puberty It usually is caused by either *Microsporum audouini* or *Microsporum lanosum* The latter type is inflammatory as a rule and may eventuate in kerion The former type produces the indolent gray patch type of ringworm of the scalp Infected hairs of either produce bright greenish fluorescence under Wood s light which permits one to follow the progress of treatment Intelligent management of tinea capitis requires examination under this filtered ultraviolet light and identification of the causative organism which may be undertaken by culturing the infected hairs on Sabouraud s agar

Local Treatment

Local therapy and manual epilation of infected hairs almost invariably effects a cure in the animal type of infection caused by *M lanosum* but usually fails in the human type caused by *M audouini* Roentgen ray epilation is the best and quickest method for the cure of *M audouini* infection and is safely performed by experts Defluvium occurs in about three weeks and is followed by regrowth of hair in a month or two During this period the patient is observed periodically and any *remaining* fluorescent hairs are manually epilated Topical therapy using mild fungicidal remedies also is carried out concurrently

Diseases Due to Fungi

DERMATOPHYTOSIS

Dermatophytosis is a superficial fungous infection of the intertriginous or flat areas of the skin It includes tinea pedis, tinea manuum and allergic manifestations or dermatophytids Onychomycosis is frequently present and usually affects the toe nails While identification of the causative fungus is desirable, it is not imperative for successful treatment The clinical manifestations of the disease provide a helpful guide to appropriate treatment Self medication and overtreatment of dermatophytosis is so common that the presenting picture is often that of a severe contact dermatitis

Acute Vesiculobullous Dermatophytosis

In the acute vesiculobullous form management is similar to that for any acute eczematous process Wet dressings or soaks are indicated These may be used continuously or intermittently according to the severity of the process Suitable preparations are 2 per cent boric acid solution 1 6000 potassium permanganate solution or 1 30 aluminum acetate solution With diminution of the exudative phase a soothing paste is prescribed for application between wet dressings and at bedtime An example of a suitable preparation is the following

	Gm or cc
Icthammol	1
Liquid petrolatum	8
Zinc oxide paste to make	30

When the acute inflammatory process subsides, 1 per cent salicylic acid can be added to the preceding formula, and wet dressings or soaks are used less frequently Benzoic and salicylic acid ointment (Whitfield s ointment) one quarter strength may be substituted upon the disappearance of all signs of acute inflammation It is applied at bedtime and removed in the morning with mineral oil This is followed by thorough washing with soap and water The following dusting powder is applied every morning to the cleansed feet

	Gm or cc
Phenol	0 18
Menthol	0 06
Salicylic acid	0 6
Magnesium carbonate	2
Boric acid	2
Bentonite	4
Talc to make	30

Sodium propionate, 12 per cent, may be included in the ointment and powder to enhance their fungicidal properties New fungicidal preparations are appearing almost daily The foregoing is sufficient to control almost all cases of dermatophytosis

Chronic Intertriginous Dermatophytosis

In the chronic intertriginous or noninflammatory type of dermatophytosis, therapy may be begun with the use of the above powder and one quarter strength Whitfield s ointment It may be desirable to increase the latter to one half strength if it can be tolerated For the chronic hyperkeratotic form of the disease it may be necessary to use the full strength ointment in the involved areas

Gentian violet 1–2 per cent aqueous solution is helpful particularly in the intertriginous forms of the disease It is applied to the affected areas several times a week

Pyoderma cellulitis lymphangitis and lymphadenitis may be complications of the acute phase and may require continuous wet dressings elevation and rest of the affected parts, and the use of penicillin aureomycin, terramycin, or the sulfonamides

acetate solution, and a mild paste such as zinc oxide paste are indicated When the acute process has subsided, antifungal remedies may be substituted

TINEA VERSICOLOR

Tinea versicolor produces brownish fur faceous patches usually on the upper trunk and neck In tanned persons, these areas appear *depigmented* The *lesions* are treated effectively by the application of 10 per cent aqueous solution of sodium hyposulfite once or twice a day One quarter strength Whitfield s ointment is equally satisfactory

Clothing, particularly underclothing should be washed thoroughly or dry cleaned to disinfect them Treatment should be continued for several months to prevent recurrence The pseudo achromic patches undergo no visible change and the patient should be so advised in advance However, peeling treatment with the cold quartz mercury vapor lamp, or tanning with the hot quartz lamp are effective in equalizing the pigmentary inequalities

MONILIASIS

The generalized and systemic forms of moniliasis are rare and need not be included in this discussion The localized forms are common and include onychia and paronychia intertrigo erosio interdigitalis blastomycetica perlèche intraoral thrush *superficial glossitis vaginitis* and *pruritus ani* It is always essential before undertaking [illegible] by [illegible] istry

The most effective single therapeutic agent in the localized forms is 1 or 2 per *cent aqueous* gentian violet Other effective fungicidal preparations are mild tincture of iodine and one quarter strength Whitfield s ointment The solution of gentian violet may be applied directly to the skin or mucous membranes or applied in suppositories (0 12 Gm of gentian violet in each suppository) in the treatment of vaginitis or pruritus ani due to monilia Where acute inflammation is present, wet dressings of potassium permanganate (1 5000) should be used In paronychia and erosio interdigitalis blastomycetica exposure to soap and water should be minimized

National Formulary antiseptic solution or sodium perborate may be prescribed as a mouth wash in perlèche or intraoral thrush A few applications of 2 per cent aqueous gentian violet will hasten involution Riboflavin in 5–10 mg doses three times daily should be prescribed because occasionally there is an associated vitamin deficiency with intraoral moniliasis Ill fitting dentures may be a contributory factor in perlèche due to the dribbling of saliva

Roentgen ray therapy in doses of 75 r at weekly intervals for a total of four to eight treatments is useful in the treatment of most manifestations of moniliasis and may be employed in resistant cases but not as *a routine procedure*

The obese patient with intertrigo complicated by moniliasis should be placed upon a weight reduction diet as well as on specific therapy for moniliasis

ACTINOMYCOSIS

Actinomycosis or lumpy jaw is a deep mycotic infection It may be localized or systemic and *it involves* the head and neck abdominal organs or other organs including the skin *Primary actinomycosis of the* skin is rare Diagnosis depends on the demonstration of the ray fungus

The treatment of actinomycosis consists of the combined use of penicillin sulfadiazine and roentgen rays The dose of the drugs should be high and the treatment prolonged Penicillin should be administered in doses of 300 000–600 000 units daily and sulfadiazine in doses of 4–6 Gm daily later reduced to 2 Gm daily The

Stimulating antiseptic ointments are used in the treatment of *M lanosum* infections The scalp is thoroughly washed with soap and water daily, and the ointment rubbed into the entire scalp morning and night The preparation may contain mercury, sulfur, salicylic acid, thymol, iodine, sodium propionate, asterol, salicylanilid other fatty acids or their derivatives or several of these in combination Mercury and iodine, or sulfur and ammoniated mercury should not be prescribed simultaneously because of incompatibility Manual epilation of fluorescent hairs is carried out at frequent intervals usually weekly, in the physician's office It may be desirable when there is widespread infection for the parents to supplement this procedure at home by using an inexpensive bulb (Purple X) This bulb produces less intense but definite fluorescence of the infected hairs However, it must be employed with caution because it becomes hot within a few minutes

Since an intense inflammatory reaction is marked by rapid defluvium and resolution of *M lanosum* infections, it is desirable to gradually increase the strength of the medicaments to effect this response However, severe kerionic reaction is to be avoided since the destruction of the hair follicles will cause permanent alopecia It may be necessary, therefore, to temper a marked inflammatory response with soothing wet dressings and to discontinue stimulating ointments Some of the newer fatty acids have been found to be effective for the treatment of both the animal and human types of scalp ringworm

A suitable ointment for the treatment of tinea capitis is the following

	Gm or cc
Salicylic acid	0 6
Ammoniated mercury	1 8
Sodium propionate	3 6
Wool fat and petrolatum each in sufficient quantity to make	30

Education of the parents regarding the infectious nature of this disease is essential The hair is clipped short every two weeks and the waste is burned The clippers are sterilized in alcohol or hot oil to prevent spread of the infection and contaminated head wear is discarded

Many communities do not permit infected children to attend school until they are cured of the infection Two negative examinations under the Wood s light, one week apart, is usually a satisfactory criterion of cure

Prophylaxis

To prevent ringworm of the scalp, contacts with infected animals and humans must be scrupulously avoided Treatment of every known case of tinea capitis must be instituted early and with the most effective methods known The problem of treatment arises in cases of infections with the *M audouini* These cases should be treated as soon as the clinical diagnosis is confirmed by cultural studies with a temporary epilating dose of roentgen rays applied by one with knowledge and experience of this procedure When the disease is of epidemic proportion the best prophylaxis is the care of the largest percentage of cases in the shortest time possible In the meantime strict isolation is advisable until a cure is accomplished

TINEA CIRCINATA

Tinea circinata is the classic form of ringworm characterized by a ringed lesion with a vesicular border and clear center It responds readily to daily painting with 1 per cent tincture of iodine, or the application of one-quarter strength Whitfield s ointment or 5 to 10 per cent ammoniated mercury or sulfur ointment

In the eczematous type where the inflammation may be due to the particular causative organism or to a superimposed contact dermatitis, wet compresses of 2 per cent boric acid solution and/or 1 30 aluminum

COCCIDIOIDOMYCOSIS

Coccidioidomycosis may occur as a primary pulmonary form simulating influenza bronchopneumonia or even early tuberculosis In this form the cutaneous lesions may resemble erythema nodosum or erythema multiforme The progressive, disseminated systemic form of the disease may affect any part of the body Cutaneous lesions may be primary or secondary and consist of nodules tumors abscesses and ulcers Scrofulodermic lesions are sometimes present Diagnosis is dependent upon the demonstration of the organisms by direct examination of pus or tissue, or by their culture

The treatment of primary coccidioido-
mycosis consists of bed rest u
ature leukocyte count and the
sedimentation rate become nor
genologic findings should reveal
before the patient is discharged
the prognosis in progressive co
mycosis is almost invariably hop
portive therapy in the form of res
diet and vitamins should be pr
Jacobson has recommended the
special extract of the organisms a
intramuscular injection of colloidal c
Antimony and potassium tartrate, th
and other drugs are ineffective Pen
may be useful in overcoming secondar
fection Roentgen therapy may pro
healing of local lesions

*Diseases Due to Animal Parasites**

PEDICULOSIS (CAPITIS, CORPORIS AND PUBIS)

Pediculosis or infestation with lice may affect the scalp body or genital region Occasionally the eyebrows eyelashes and axillary hair become involved In pediculosis capitis and pediculosis pubis the parasites and ova are found in the affected areas In pediculosis corporis the parasite must be sought in the seams of the clothing

Pruritus is intense in all forms of the infestation In pediculosis corporis although the parasite may not be demonstrable characteristic findings are parallel scratch marks and excoriations covered by dried bloody crusts distributed on the shoulders buttocks and external thighs

The number of remedies suggested for the treatment of pediculosis capitis is legion Larkspur tincture equal parts of kerosene and olive oil and a 1 1000 solution of mercury bichloride are among the time honored measures Newer medicaments are too numerous to mention fully A mixture of DDT, benzocaine benzyl benzoate and a wetting agent (NBIN) is recommended by the U S Department of Agriculture A simple and effective method is the use of undiluted benzyl benzoate lotion (25 per cent emulsion of benzyl benzoate) The hair and scalp first are washed thoroughly with soap and warm water The lotion is then applied to the scalp and hair with a gauze pad and rubbed in with the fingers The patient is admonished to prevent the solution from coming in contact with the eyes The hair is combed and allowed to dry A towel is then wrapped around the head Twenty four hours later the head is thoroughly washed with soap and water and combed with a fine comb The treatment may be repeated if necessary The benzyl benzoate emulsion is the preferred treatment because it is effectual easily applied and inoffensive

The impetiginous lesions of the glabrous skin so frequently associated with pedi-

* See also Chapter 9

successful oral use of diasone in the treatment of actinomycosis has been reported Filtered roentgen rays, closely shielded should be administered by an expert in large destructive doses applied to the involved areas Up to 3000–5000 r may be necessary to destroy some lesions employing voltages up to 200 Kv and a filter of 5 mm Cu The total dose is administered in a period of two to four weeks Accessible lesions may be excised or incised to provide adequate drainage The sinuses may be irrigated with diluted Lugol s solution or 1 per cent aqueous solution of gentian violet Aureomycin, streptomycin and potassium iodide solution are also valuable

BLASTOMYCOSIS

Blastomycosis (North American) is a deep mycotic infection which may be local or systemic. In the majority of cases the initial lesion appears as a papulopustule on the skin A characteristic verrucous patch is formed from which the causative yeastlike organism may be isolated In the systemic form, any organ may be involved, but the lungs are the most common site

Surgical excision of the cutaneous lesion should be undertaken when feasible Filtered roentgen rays as for actinomycosis should be administered to lesions not suitable for excision Large doses of a saturated solution of potassium iodide are prescribed The initial dose is 15 drops three times daily after meals this is increased gradually until symptoms of intolerance appear The maximum dose that can be tolerated is then adhered to for months or even years in some cases Sodium iodide intravenously in doses of 1 Gm may be used as may ethyl iodide inhalations Desensitization with blastomyces vaccine prior to initiation of iodide therapy is advocated by some Supportive measures are of particular importance in the systemic form of the disease Recently there have been reports that blastomycosis responds well to treatment with diethyl stilbestrol and to stilbamidine

SPOROTRICHOSIS

Sporotrichosis is a chronic, deep mycotic infection due to *Sporotrichium schenkii* It is characterized by the presence of cutaneous and subcutaneous nodules, abscesses and ulcers in linear formation along the course of the lymphatics and usually appearing on the upper extremities Several types of the disease occur the localized lymphangitic type, disseminated subcutaneous type, disseminated ulcerating type epidermal type, and systemic type The diagnosis is readily made by culturing the organism

Potassium iodide is virtually a specific in the treatment of this disease Fifteen drops of a saturated solution of potassium iodide three times daily are prescribed initially The dose is rapidly increased until the limit of tolerance is reached It may be diluted in milk or water The drug should be continued for several weeks after the patient has apparently recovered to minimize recurrences Sodium iodide 1 Gm daily intravenously may be substituted for the orally administered iodide if the latter is poorly tolerated

Roentgen rays unfiltered or lightly filtered may be useful in the treatment of individual lesions if used in conjunction with iodide therapy

Surgery other than aspiration of pus for culture or drainage is contraindicated as indolent ulceration supervenes For open lesions wet dressings with aluminum acetate solution or potassium permanganate solution (1 4000) may be employed Two per cent aqueous solution of gentian violet or half strength Lugol s solution may be used to irrigate the lesions

Vaccines, autogenous or stock, may be used as supplementary treatment Penicillin and streptomycin are ineffectual

with certain endemic areas—notably along the southeastern seaboard The parasite forms bizarre patterns often simulating a relief map The configurations change from day to day

Treatment may be local or systemic Local treatment consists of destruction of the larvae by freezing This is accomplished by applying to the advancing end of the lesion solid carbon dioxide, liquid nitrogen or ethyl chloride spray until the skin is frozen Unless a blister is raised the larva is not destroyed and may be stimulated to further activity Several treatments may be necessary, but the method is effective for treating cases where only a few larval trails are present

Systemic treatment with 'fuadin intramuscularly, in 5 cc doses daily, has been used with inconsistent results in patients with extensive infestations Oxophenarsine hydrochloride at three to five-day intervals 0 06 Gm intravenously, for adults (smaller doses for children), has been effective after administering from 1 to 9 injections according to Hitch Van De Erve, Jr found hetrazan (1 diethylcarbamyl 4 methylpiperazine hydrochloride) in doses of 2 mg per kg body weight administered three times daily, preferably after meals to be promising The dosage was the same regardless of age and significant toxic side-effects were not observed Oral administration was used with effective larvistasis in forty eight hours cure occurring in from seven to ten days

The Eczemas

THE word eczema signifies an exudative eruption There is usually erythema, vesiculation exudation and exfoliation or crusting Any part of the body may be affected, and the clinical signs vary so that many adjectives have been used to differentiate one clinical variety from another Some of the terms which have been used are *eczema erythematosum pustulosum lichenoides* and *verrucosum* Eczema may be of internal or of external origin or a combination of the two and there are not any clinical differences among these various etiologic types In many cases of eczema there is an internal sensitization factor plus a local exciting factor A possible exception are eczematous eruptions caused by contact with known irritants The term dermatitis is often used synonymously with eczema

NEURODERMATITIS

There are two main types of neurodermatitis the circumscribed and the generalized The circumscribed disseminate variety consists of one or more sharply circumscribed patches with predilection for the flexors of elbows, knees, sides and back of neck and inner surfaces of the thighs The patches are dry, scaly, thickened and lichenified The itching is intense and often scratch marks are severe They tend to be chronic and stubborn

Localized Neurodermatitis

Localized neurodermatitis responds exceptionally well to four weekly treatments of 75 r each of low voltage (100 kv) unfiltered roentgen rays In many instances improvement can be obtained by the oral administration of one of the antihistaminics given in divided doses three or four times daily The local use of an antihistaminic ointment has been valuable in allaying the severe pruritus in very few cases The use of a tar preparation such as crude coal tar oil of cade or one of the tar distillates in concentrations of 3–12 per cent in zinc oxide

culosis capitis, may be treated with ammoniated mercury ointment

One application of benzoate emulsion to the affected areas usually is sufficient to eradicate pediculosis pubis, but it may be repeated for several nights to ensure this result Ten per cent DDT powder also is effective When the eyelashes are involved strong parasiticides are contraindicated and the lice and ova must be removed with fine forceps Ophthalmic yellow mercuric oxide ointment, 2 per cent, is effective in killing the lice on the eyelashes

Treatment of pediculosis corporis requires little more than the sterilization of clothing by boiling or dry cleaning and a soap and water bath for the patient An antipruritic lotion such as the phenolated calamine lotion may be prescribed for residual symptoms Delousing of clothing or personnel may also be effected by the use of 3–10 per cent DDT solution or a powder of 10 per cent DDT in talc

SCABIES

The diagnosis of scabies does not present a problem when the lesions are typical in distribution and other members of the household suffer from the same intractable pruritus However, in clean individuals, the paucity of lesions may render the diagnosis difficult In these individuals in the absence of any other cause for generalized pruritus such as diabetes mellitus, hepatic or renal disorder, blood dyscrasia etc, treatment for scabies should be undertaken as a therapeutic test

The treatment of scabies like that of pediculosis has undergone many modifications in recent years because of the advent of new drugs Nevertheless, precipitated sulfur, Peruvian balsam, and benzyl benzoate can be relied upon to eradicate the disease in a relatively short period of time NBIN has been recommended by the U S Department of Agriculture and many effective proprietary antiscabetic agents, such as Kwell,' also are available

Benzyl benzoate lotion (25 per cent) is applied from the neck to the toes by hand or with a small paint brush, following a warm soap and water bath Particular attention is given to the application of the lotion in the areas of predilection, such as the finger webs, elbows, axillae, and intergluteal fold The lotion is permitted to dry and is then reapplied Twenty four hours later another bath is taken and this time clean clothes are donned The bed linens and clothing are sterilized by boiling or dry cleaning All members of the household should be treated simultaneously if the disease is suspected in them

An ointment of 10 per cent precipitated sulfur in petrolatum is equally effective, but it must be applied nightly for three nights A bath is taken before treatment is begun and again on the fourth night At this time all clothes and sheets are changed and sterilized as previously described

Children tolerate 5 per cent Peruvian balsam and 5 per cent precipitated sulfur in petrolatum more satisfactorily than the 10 per cent sulfur ointment or benzyl benzoate lotion For young children and infants precipitated sulfur powder sprinkled on the body and between the sheets may be the least irritating remedy

If the pruritus is persistent for more than a few days following treatment a soothing antipruritic lotion usually will be sufficient to overcome any dermatitis incident to the treatment If the pruritus continues a second course of therapy is indicated Where treatment has been adequate and eczematization is severe soothing baths of starch sodium bicarbonate, bran or potassium permanganate should be prescribed

LARVA MIGRANS

Larva migrans or creeping eruption is easily distinguished from scabies by the length of the burrow and by its association

wool and furs nail polish bleaching agents and medicinal preparations

The treatment of contact dermatitis requires the detection of the causative agent its removal and the application of soothing preparations to the skin such as 2 per cent boric acid solution if vesicles are numerous or exudation profuse Otherwise applications of boric acid ointment or zinc paste are sufficient The more extensive cases require soothing baths using starch or bran and avoiding the use of soap The oral administration of antihistaminics such as pyribenzamine or neo antergan is valuable in controlling the pruritus

Many cases of poison ivy dermatitis are made worse by overzealous treatment and by the use of poison ivy extracts There is no unequivocal evidence to substantiate the claim that injections of poison ivy extract prevents or shortens the course of poison ivy dermatitis Some severe generalized cases of contact dermatitis are improved by the administration for a day or two of 0 2–0 3 Gm of cortisone by injection or by mouth

DERMATITIS SEBORRHEICA

This affection is most frequently encountered on the scalp ears face chest and upper back It is also seen in the groin and axillas Severe dandruff is probably a type of seborrheic dermatitis The eruption occurs in patches is characterized by greasy scales and is yellowish red to brown in color In the intertriginous areas it is exudative and may be complicated by a monilial infection

The scalp should be washed daily with soap and water A few applications of an ointment containing 2 per cent salicylic acid and 6 per cent ammoniated mercury in a greaseless base are usually sufficient to control many cases affecting the scalp For the eruption on the nonhairy parts of the skin an ointment containing 6 per cent ammoniated mercury suffices The eruption also responds to sulfur or tar preparations

If the axillas and groin are involved and the lesions are moist a few applications of 2 per cent gentian violet preceding the ointment treatment is advisable. There are instances, however, where the disease seems intractable, and the treatment measures must be varied considerably even to attain control Even roentgen therapy in doses of 75 r may be necessary in stubborn cases

REGIONAL DERMATITIS

Eczema of the Breasts

Eczema of the breasts especially of the nipples is sometimes confused with Paget's disease of the breast Eczema in this location may be unilateral or bilateral and is usually a manifestation of a chronic contact dermatitis due to sensitivity to fabrics of which brassières are made cosmetics (perfumes toilet water) the frequent use of soap or to friction Soothing and protective treatment with zinc oxide paste and cleansing with mineral oil will be sufficient in many instances Of course the offending agent must be removed In some instances eczema of the breasts is a localized manifestation of neurodermatitis (atopic dermatitis) in which case treatment is the same as that for localized neurodermatitis of other areas Superficial roentgen ray therapy is the only effectual treatment in recalcitrant cases A dose of 75 r of low voltage (100 Kv) unfiltered roentgen rays given once a week for four to eight treatments usually suffices

Eczema of the Hands

Eczema of the hands is one of the most troublesome conditions to treat because the cause is not always easily ascertainable In most instances the patient has an allergic background and contact with even mild irritants can produce severe manifestations of eczema

The treatment in general is the same as for localized neurodermatitis except that

paste causes many lesions to disappear The addition of 1 per cent phenol is helpful Elimination diets are helpful in an occasional case Skin tests are of limited usefulness Contact irritants such as soap, wool, unsuitable medicines, and friction are to be avoided

Generalized Neurodermatitis

The generalized type of neurodermatitis is a more severe problem and is seen in both infants and adults In some instances the entire body is covered with crusted exuding and lichenified lesions In infants, foods and local irritants are the exciting agents in most instances In adults the etiologic factors are more insidious In many adults and even children psychiatric disturbances are responsible for acute exacerbations

The *treatment* of the generalized variety of neurodermatitis is more or less the same as that of the localized variety Roentgen ray therapy should be avoided or reserved for recalcitrant cases For it can be substituted ultraviolet ray therapy in suberythema doses Daily exposures are definitely valuable Baths are very soothing and if there is not any evidence of secondary infection the bath can consist of only warm water or there may be added a cup each of starch and sodium bicarbonate Oatmeal or bran may be used, but these have to be enclosed in cheese cloth If there is infection present 10 0 3 Gm tablets of potassium permanganate may be added to the tub of water Friction in the tub and in drying is to be avoided After the bath a soothing emulsion such as the following applied to the entire body gives relief

	Gm or cc
Anhydrous lanolin	50
Olive oil	100
Zinc oxide	50
Starch	50
Tragacanth	4
Aluminum acetate solution	6
Lime water to make	500

To this may be added 3–12 per cent cade oil The exudative areas must be treated with continuous wet compresses of 2 per cent boric acid solution during the day and the liberal use of petrolatum during the sleeping hours

Suggestive therapy and change of environment may be recommended in some cases Antihistaminic preparations taken by mouth have been helpful in some cases The more severe cases require sedation for it is of the utmost importance that patients get the required sleep each day Foods that provoke itching have to be avoided, but the nutrition of the individual must not be sacrificed Good general health must be maintained Especially severe and recalcitrant cases require the combined specialized knowledge of an allergist, a psychiatrist, an internist, and a dermatologist under strict hospital supervision where the environment is under constant control

Severe cases of neurodermatitis are sometimes very recalcitrant In such cases, *ACTH* or *cortisone* may be used After a few days the itching and the objective symptoms become markedly improved About 25 mg of cortisone are administered by mouth every four to six hours As soon as the eruption improves the cortisone may be discontinued and conventional antieczematous treatment is continued

CONTACT DERMATITIS

The cause of contact dermatitis is usually some substance to which a person is sensitive The sites of predilection are the hands, forearms neck, and face, but any part of the body that has come in contact with the offending substance may be affected. The eruption is characterized by erythema and vesicle formation with intense pruritus In chronic cases the skin is thickened, scaly, and fissured Some of the many common causes of contact dermatitis are poison ivy, primrose, soap, detergents, lacquers, cosmetic preparations, dyes, fabrics such as

starch, and a soothing preparation such as the calamine lotion should be prescribed Ointments should be avoided as they cause maceration Fissures may be painted with 5 per cent silver nitrate solution or 1 per cent aqueous gentian violet The latter remedy is particularly effective when monilia infection is present

The Erythemas

THE erythema group of skin diseases has a sudden onset, rapid evolution, and short duration and is characterized by erythema, edema and sometimes exudation For the most part they are of toxic origin The noxious substance may be a drug bacteria, or a protein sensitization

URTICARIA

The successful management of urticaria requires thorough and exhaustive inquiry into the possible causative factors In acute urticaria, investigation will frequently disclose a history of ingestion of a food to which the patient is allergic or of recent use of a drug such as penicillin, barbiturates, sulfonamides salicylates, or quinine Other urticariogenic allergens such as inhalants often are implicated Foci of infection, parasitic infestation, physical agents visceral disease, or emotional and nervous factors are less frequently encountered as the cause In acute urticaria the eliciting agent usually can be discovered only by painstaking study of the patient and his habits A thorough history and physical examination therefore are indispensable However, in chronic urticaria it is only rarely possible to determine the causative allergen Skin tests usually are not helpful

Treatment

Treatment of urticaria should begin with the elimination of the cause if possible The patient is instructed to stop all drug intake Foods which are known to be common urticariogenic agents are eliminated from the diet These include pork, veal, fish nuts, chocolate, tomatoes strawberries, cheese, and cabbage in the adult. In children wheat, eggs and milk also are interdicted Rigorous elimination diets sometimes are indicated A saline cathartic may be administered initially Antihistaminic medication is prescribed, 0 1–0 2 Gm daily of "neo-antergan" in divided doses orally usually being sufficient to alleviate the pruritus although urticarial lesions may appear unabated

Lukewarm baths to which a cup of hydrolized starch ('linit') and a cup of sodium bicarbonate have been added are soothing A soothing emulsion or the phenolated calamine lotion may be applied to the affected areas

Although the advent of the antihistaminic drugs has diminished the popularity of the sympathomimetic drugs the latter may prove exceedingly useful in some instances For example, epinephrine injection in 0 5 cc. doses or ephedrine sulfate 25 mg, every three or four hours may be prescribed

Histamine protein injections subcutaneously in ascending doses may be helpful in chronic and recurrent cases Calcium gluconate, 1 Gm intravenously, is also a useful adjuvant and may be administered several times a week Cortisone and ACTH are often efficacious in the treatment of acute urticaria following penicillin *

Chronic Urticaria

Acute urticaria will respond readily to the above regimen However, chronic urticaria may present considerable difficulty

* See also Chapter 21

search for causative factors must be carried out more diligently Even the use of mild soap can precipitate a severe attack For many women the precipitating cause is traceable to a cosmetic, a household cleaning agent an insect repellent, or even the handling of food such as oranges For workmen the cause is usually something found in his shop such as oils detergents and dyes and for dentists and physicians substances such as procaine, adhesive, rubber gloves, and sterilizing solutions are common offenders Eczema of the hands can be extremely handicapping It may prevent a dentist from doing his work or a surgeon from operating A cosmetician or an operator in a hairdressing salon may be so allergic to the substances in his work that he has to learn a new trade

Eczema of the Legs

In this location the eczema is often secondary to impaired peripheral circulation The eczematous eruption of the legs is often complicated by excoriations and varicose veins and ulcers

The treatment is directed towards improving the circulation either by venous ligations or by the injection of sclerosing solutions In addition to local appropriate antieczematous treatment such as already outlined, it is necessary to elevate the lower extremities or wear elastic stockings or elastic bandages or use gelatin bandages In these cases special attention must be given to interdigital dermatophytosis regardless of how mild it is

Eczema of the Scrotum

The localized form of neurodermatitis sometimes affects the scrotum, causing it to become edematous and lichenified As a result the scrotum assumes twice or three times its normal size There usually is exudation and crusting and the pruritus is sometimes unbearable

The treatment is soothing with the employment of boric acid compresses sitz baths, and applications of zinc paste Use of antihistaminics such as "neo-antergan" in 50 mg doses three or four times a day helps to allay subjective symptoms At times roentgen ray therapy is the only agent to control the severe pruritus A nonpenetrating type of radiation such as grenz rays or radiations from a beryllium window tube should be used in order to protect the underlying testicles Doses of 75–100 r once a week for a total of four treatments usually suffices

INTERTRIGO

Intertrigo is an inflammatory disease which affects apposed surfaces of the body such as the groin, the axillas inframammary regions and the intergluteal cleft Manifestations vary from erythema to marked exudation, maceration, and painful fissuring The disease is more common in obese individuals and during the warm months of the year in temperate zones Retained perspiration and friction are the precipitating elements Monilial infection is a frequent complication and diabetes mellitus may also be associated

The disease must be differentiated from such common dermatoses as seborrheic dermatitis, psoriasis and dermatophytosis For the relief of intertrigo irritating or sensitizing remedies are sometimes used and so contact dermatitis is a frequent complication of intertrigo

Treatment should be directed against the underlying causes Weight loss should be encouraged in the obese Meticulous hygiene with frequent bathing and the use of a dusting powder such as talc or fuller s earth is helpful to prevent recurrences Underclothing should be loose fitting to encourage evaporation of perspiration The acute episode is managed similarly to any acute dermatitis Wet dressings of 2 per cent boric acid solution, baths with "linit

mild or severe Probably any drug with the exception of the salines can produce a rash in a susceptible individual The list of drugs that can produce an eruption and their individual characteristics is so extensive that a complete description cannot be undertaken in a single chapter

Dermatitis medicamentosa is a polymorphous eruption The size, shape and distribution of the lesions vary They may be erythamatous papular, pustular, vesicular gangrenous purpuric, urticarial or pigmented or any combination of these types There are no particular sites of predilections

Treatment

The treatment of drug eruptions requires suspicion that a particular rash is caused by a drug Only careful questioning will permit determination of the responsible drug When the offending drug is eliminated improvement soon ensues In many instances nothing more is needed

If there is excessive pruritus starch and sodium bicarbonate baths are soothing and a shake lotion such as calamine lotion with 1 per cent phenol will temporarily allay the itching Antihistaminics such as neo-antergan *also aid in controlling subjective* symptoms Those who are allergic to penicillin develop an urticarial eruption which may not be controlled easily with the antihistaminics In such instances ephedrine by mouth or epinephrine by injection may be necessary Autohemotherapy and calcium gluconate intravenously are of questionable value Cortisone and ACTH often cause quick involution of drug eruptions

Miscellaneous Conditions

APHTHOUS STOMATITIS

Aphthous stomatitis is characterized by the presence of vesicular lesions of the oral mucous membrane which become eroded and superficially ulcerated They commonly *are known as canker sores* and are painful

The disease is probably caused by a virus but certain trigger factors seem to play an important role These may be foods trauma infection or neurogenic factors

Local treatment consists of the use of a mouth wash such as the N F antiseptic solution or a saline solution several times a day Painting the lesions with a mild caustic for example two per cent silver nitrate chromic acid or copper sulfate solution is beneficial Healing usually occurs within a week or two Aureomycin troches and aureomycin or terramycin orally expedites cure

The use of smallpox vaccine administered by repeated vaccination or intradermal injection has been advocated for the treatment of recurrent cases The elimination of trigger factors will minimize recurrences

CUTANEOUS HORNS

Cutaneous horns are conical projections irregularly shaped varying in size from a few millimeters to many centimeters and yellowish to dark brown in color The lesions are usually single but may be multiple Sites of predilection are the face scalp and hands less frequently the penis scrotum and buttocks Malignant degeneration frequently occurs at the base in the form of basal or squamous cell carcinoma

Because of the precancerous nature of the lesion every cutaneous horn should be destroyed completely The lesion should be

and will require continual efforts directed towards the elimination of foci of infection correction of psychosomatic problems avoidance of physical causes or any other potential etiologic factor The treatment outlined will serve as satisfactory symptomatic treatment for these cases We cannot help but emphasize the role that emotional disturbances play in the cause of many chronic cases of urticaria *

ERYTHEMA MULTIFORME

Erythema multiforme is an acute inflammatory disease characterized by multiform lesions (macules papules or nodules vesicles or bullae and rarely pustules) The idiopathic form of the disease tends to be recurrent in the spring and autumn and runs its course in a few days to a few weeks It is usually limited to the hands forearms face and neck and requires little or no treatment The symptomatic type however presents much the same problem as urticaria since drugs infection or visceral disease may be the cause The management is similar to that of urticaria

Ectodermosis erosiva pluriorificialis (Stevens Johnson s disease) is a form of erythema multiforme bullosum in which there is severe ocular involvement and where ophthalmologic consultation is mandatory

In general the subjective symptoms are

* See also Chapter 23

mild in erythema multiforme Soothing colloid baths of starch and the application of a phenolated lanolin emulsion or a shake lotion are satisfactory symptomatic treatment Here as in urticaria the search for the precipitating factor is the essential feature

CHILBLAINS

Acute chilblains are equivalent to the very earliest stage of acute frostbite * They occur on the hands and feet of susceptible individuals in cold and damp climates and are characterized by a discoloration and sometimes by a cyanotic tint Tenderness itching and burning are present The parts are cool and usually moist With repeated exposure to cold and dampness a susceptible individual may develop chronic pernio with ulcerative lesions resembling Raynaud s disease

Treatment of pernio consists in the protection of the exposed area from trauma and exposure to heat greater than 85° F local stimulants and brisk rubbing is to be avoided Warmer clothing should be worn to prevent recurrences and if necessary removal to a warmer climate should be advised to prevent chronic chilblains Peripheral vasodilators such as niacin or priscoline may effect a valuable improvement of the circulation

* See also Chapters 11 and 25

Drug Eruptions

DERMATITIS MEDICAMENTOSA

This entity includes all mucosal or cutaneous manifestations caused by a drug regardless of whether the drug is taken by mouth injection inhalation external contact or a combination of these routes The acne-like pustules which develop in a susceptible individual following the ingestion of bromides serve as an example of dermatitis medicamentosa The clinical characteristics of drug eruptions vary with the drug ingested The same clinical characteristics are sometimes observed when different drugs are ingested or injected

The eruption may be localized or generalized and the subjective symptoms may be

calamine lotion or emulsion temporarily relieve the intense itching

HERPES SIMPLEX

Herpes simplex is characterized by the appearance of grouped vesicles on an inflammatory base accompanied by subjective symptoms of heat and burning The areas affected are usually the face or the genitalia The disease is believed to be of virus origin It may accompany febrile diseases such as pneumonia malaria and cerebrospinal meningitis Exposure to sun trauma, foci of infection gastrointestinal disorders, and other factors seems to play a role Recurrence is common

Treatment

Treatment is relatively simple Wet compresses of boric acid or aluminum acetate solution are comforting when the subjective symptoms are marked Mild astringent solutions such as 2 per cent tannic acid or compound benzoin tincture are helpful Crusts may be softened by the application of boric acid ointment Some patients prefer camphor ice or spirits of camphor for the relief of symptoms

Recurrent herpes simplex presents a distressing problem Small doses of roentgen rays to the site of recurrence is advocated by some One of the most beneficial methods for preventing recurrences is that of attempting to eliminate all possible causative factors and performing repeated vaccinations Vaccination with ordinary smallpox vaccine is done regardless of whether a 'take' occurs or not, at one to two week intervals for from four to six treatments The course may be repeated if necessary

Patients with an eruption of the skin such as eczema should not be vaccinated because of the possibility that eczema vaccinatum might develop Furthermore, vaccinations are not entirely safe and it may be advisable to endure the nuisance of a small localized rash to which zinc oxide ointment might be applied than to risk the development of complications following repeated vaccinations

HERPES ZOSTER

Herpes zoster is an acute disorder characterized by the presence of vesicles on an inflammatory base The associated pain unilateral distribution (usually), failure of recurrence (usually), and location along the course of the affected nerve distinguish it from herpes simplex

There are two types of herpes zoster The primary idiopathic variety is caused by a neurotropic virus The secondary type may be associated with infection, trauma, drugs lymphoblastomas, or chemical intoxication A thorough history and physical examination are essential in order to determine whether any of these factors are implicated

Treatment

Soothing and antipruritic lotions or emulsions are used for local treatment Wet dressings may be indicated in bullous or gangrenous forms Painting the area with collodion sometimes aborts early lesions Spraying with paraffin is advocated by some for relief of local symptoms

Pain The pain of herpes zoster is usually the most distressing feature of the disease Analgesics such as codeine and acetylsalicylic acid are frequently necessary to relieve the neuralgic pain Thiamine chloride in doses of 0 1 Gm administered parenterally every day or two often yields *beneficial results*

Posterior pituitary injection ('obstetrical) administered intramuscularly in doses of 0 5–1 0 cc every two days for several doses will sometimes effect dramatic relief from pain cause rapid involution of the vesicles and prevent a new crop of lesions *from developing* One must be aware of the contraindications to this drug Sodium iodide, intravenously, in 1–2 Gm doses may

excised for histologic examination and the base throughly curetted and electrodesiccated

DERMATITIS EXFOLIATIVA

There are two main types of exfoliative dermatitis primary and secondary In both types the eruption is generalized or universal and is characterized by pigmentation desquamation thickening of the skin adenopathy severe pruritus and chilliness

In the *primary* type the eruption appears suddenly without apparent reason and lasts several weeks to several months Relapses are frequent

In the *secondary* type the universal dermatitis is secondary to such diseases as extensive contact dermatitis neurodermatitis psoriasis seborrheic dermatitis or lymphoblastoma It is also associated with heavy metal intoxication such as arsenic poisoning The eruption is extremely recalcitrant and some may succumb to it

Treatment

The treatment is difficult and uncertain Patients have to be hospitalized and supportive treatment administered in the form of tonics vitamins liver injections transfusions and autohemotherapy

Infected teeth and tonsils should be removed If there is evidence of infection treatment with the sulfonamides penicillin or the mycins is indicated provided the eruption is not due to these drugs Contactants must be avoided

Stimulating *topical remedies* should not be used only the more bland preparations such as mineral oil or petrolatum should be used Friction must be avoided Particularly beneficial are baths and wet packs but soap is not to be used

Treatment with *roentgen rays* in doses of 75 r once a week is of value to control the severe itching and causes involution of the cutaneous lesions Not more than 25 per cent of the body surface is to be irradiated at any one sitting However, care is required to avoid radiation effect of the hematopoietic system

ACTH and cortisone have proven to be effective drugs in the treatment of exfoliative dermatitis

After laboratory studies if it is decided that the cause of the exfoliative dermatitis is due to arsenic, intravenous sodium thiosulfate in 1 Gm doses and eliminative therapy may be of value BAL is helpful in some cases If the dermatitis is a manifestation of a lymphoblastoma intense treatment with roentgen rays of the skin and lymph node bearing areas may be undertaken, or one of the radioactive isotopes may be administered However soothing local treatment is carried on conjointly with radiation therapy Irradiation therapy of an extensive lymphoblastoma requires exacting technic and specialized knowledge that only a specialist in such diseases can adequately treat these cases

DERMATITIS HERPETIFORMIS

This disease of unknown etiology, is characterized by the appearance of groups of vesicles involving mostly the trunk When the lesions disappear they leave areas of pigmentation The eruption is extremely pruritic and runs a chronic course There are not any systemic symptoms

The *treatment* of dermatitis herpetiformis (Duhring s disease) is more efficacious now than formerly The disease responds particulary well to sulfapyridine in doses of 0 5–1 Gm three times a day and it may be continued if necessary for long periods of time (years) to prevent recurrences Terfonyl 4–6 Gm daily is helpful in cases less responsive to sulfapyridine The only other effectual drug is arsenic in some form or other The halogens appear to make the eruption worse Treatment with superficial doses of roentgen rays is beneficial in controlling severe pruritus Locally soothing baths and phenolated

deeper lesions, surgical excision may be preferable Keratoses respond to treatment with roentgen rays or radium, but one of the destructive methods is preferred When malignant degeneration is suspected, it is advisable to excise the lesion and a portion of normal surrounding skin for histologic examination Beta or gamma rays of radium or roentgen rays offer effective treatment but they are definitely contraindicated for postradiation keratoses

Patients with senile keratoses ("farmer's or "sailor's skin") should be advised to protect themselves from the sun by a head covering or a sun protective cream or lotion (see p 827) Overexposure to sunshine over a long period of time is definitely carcinogenic

LEUKOPLAKIA

This disease is not syphilitic or cancerous but it may be associated with both diseases It is a serious condition of the mucous membranes, especially of the oral mucosa It is manifested as white patches involving only a portion of the mucosa or it may be so extensive that it involves the entire mouth Superficial patches are smooth and glistening white Some of the deeper patches are verrucous and fissured and may distort the entire tongue Leukoplakia is a definite precancerous condition and should be regarded seriously

Treatment of leukoplakia depends upon the severity of the disease Bad teeth should be removed The mouth hygiene must be improved The use of tobacco must be completely stopped Spicy foods and alcohol are undesirable for an irritated mouth If syphilis is present active treatment should be instituted Large doses of vitamin B complex is definitely beneficial The larger verrucous patches must be destroyed under procaine anesthesia with either the cautery or electrodesiccation and curettage or by surgical excision

LICHEN PLANUS

Lichen planus is an inflammatory dermatosis characterized by the presence of numerous violaceous, glistening polygonal flat papules The lesions may be limited to a few areas as the flexor aspects of the wrists and forearms, and ankle regions or widespread with involvement of the oral mucous membrane Pruritus may be severe The disease frequently occurs in persons of nervous temperament who manifest symptoms of anxiety, emotional instability, or fatigue The disease may last for months or years if untreated

Treatment

Treatment of lichen planus is local and systemic. An antipruritic lotion is prescribed for the relief of local symptoms Starch sodium bicarbonate, and bran baths are useful in generalized cases

In the systemic treatment neurogenic factors should be considered Sedatives and simple psychotherapy may be employed if necessary A change of environment or a vacation at a health resort or spa may effect rapid improvement The drugs which yield optimum results are bismuth, arsenic and mercury

Bismuth subsalicylate injection, 1 cc administered intragluteally at weekly intervals should be administered for a course of about ten injections, followed by a rest period of one month and repetition of the course if necessary Potassium arsenite solution, three drops in one half glass of water after meals, may be prescribed instead of the bismuth Mercury in the form of the protiodide, 6–10 mg after meals may be substituted for either of the preceding medicaments Since the disease is sometimes stubborn all of these methods of treatment are employed one at a time before involution takes place

The most effective therapy is the combined use of low voltage (100 Kv) unfiltered superficial roentgen rays in weekly doses of

do the same Aureomycin or terramycin 0 25 Gm every six hours may be extremely effective

Unfiltered roentgen rays to the skin lesions or filtered roentgen rays in doses of 100 r administered every three days for four doses to the area of the affected posterior spinal ganglions may reduce discomfort and hasten involution of the disease In intractable pain sympathetic ganglion block is very occasionally resorted to Cobra venom also has been employed In ophthalmic zoster serious damage to the eye may result and the services of an ophthalmologist should be enlisted

KELOID

These hypertrophic scars which occur in individuals who show an idiosyncrasy are very disfiguring Some lesions appear to start spontaneously but they invariably follow trauma especially that due to burns The lesions are elevated forming bands or tumors and the skin is colored When areas such as the neck or joints are affected limitation of motion results The lesions are seen more frequently in brunettes and Negroes Keloids seldom if ever degenerate into malignant neoplasma

The best form of treatment which is effectual is radium or roentgen ray therapy Sometimes large keloids are removed surgically but the area is irradiated pre and postoperatively The superficial keloids are treated weekly with 75 r of low voltage (100 Kv) unfiltered roentgen rays for a total of eight to twelve treatments The deeper lesions are treated with filtered roentgen rays It is well not to give any one area more than 1200 r

Many keloids respond exceptionally well to treatment with solid carbon dioxide Surgical excision or other surgical procedures will result in the formation of a large keloid unless ionizing radiations are also used

KERATOSES

There are several types of keratoses—seborrheic senile chemical due to ingestion or injection of arsenic or exposure to certain tars and postradiation (sun and roentgen rays) All types usually appear in the latter decades of life

Seborrheic Keratoses

Seborrheic keratoses are of relatively little importance since they rarely if ever terminate in malignancy Removal may be desirable however for cosmetic reasons These lesions are recognized by their brownish pigmentation verrucous appearance and soft loosely adherent crusts They are stuck on the skin and are easily removed by gentle curettage followed by light cauterization of the area with a cotton swab moistened with trichloracetic acid (saturated solution) When the area begins to blanch the acid is neutralized by the application of another cotton swab wet with a saturated solution of sodium bicarbonate It may be necessary to infiltrate larger seborrheic keratoses with 1 to 2 per cent procaine solution and then to electrodesiccate and curette the lesion

Senile Chemical and Postradiation Keratoses

Senile chemical and post radiation keratoses are precancerous lesions and may eventuate in squamous cell carcinoma It is necessary that these lesions be recognized and destroyed Senile keratoses are usually found in the exposed areas of the body and present firmly adherent keratotic scales Arsenical keratoses usually occur on the palms and soles A history of industrial exposure will be elicited in cases of tar keratoses Keratotic lesions in the presence of chronic radiodermatitis suggest the diagnosis of postradiation keratoses

These keratoses are best removed by curettage followed by electrodesiccation under procaine anesthesia In some of the

tincture of iodine No scars result from such treatment and no anesthesia is required Recently sulfadiazine has been used in doses of 4 Gm per day for a week in extensive cases with success Treatment with sulfa diazine may be dangerous and we do not particularly recommend it Aureomycin administered orally is also effective Another good simple treatment is to paint the lesions with 95 per cent phenol and quickly neu tralize with alcohol

MYCOSIS FUNGOIDES

Mycosis fungoides is the most common lymphoblastoma affecting the skin Its clinical manifestations vary greatly from that resembling a generalized severely pruritic dermatitis to the development of discrete deeply ulcerated lesions The prog nosis varies with each patient Some have been kept alive for more than thirty years with appropriate therapy

Treatment

Treatment requires radiation therapy Roentgen ray therapy of the affected areas is most often used Some superficial and localized lesions respond to treatment with grenz rays and radium but these methods are definitely inferior to roentgen ray therapy The disease responds so well that all that is required in most instances is the application of 75 r of low voltage, unfiltered roentgen rays for a total of four to six treatments

The disease will recur perhaps not in the same spots and the roentgen ray treatment is then resumed again At no time must more roentgen rays be used than is abso lutely necessary to cause involution More recently patients have been treated with radioactive isotopes with temporary im provement There is still much to be learned concerning this method of treat ment

When cases become radioresistant treat ment with nitrogen mustard and tartar emetic has been beneficial in a few cases Both drugs are toxic and the results are only slightly good so that it can be said that irradiation is more effective than any chemical ever used for mycosis fungoides The administration of arsenic in one form or another has been used for years and the results have always been questionable

PEMPHIGUS

The cause of this fatal disease is not known It appears more commonly in Jews and Italians than any other racial group It is characterized by the appearance of successive crops of vesicles and bullae ap pearing suddenly on apparently normal skin The entire body may be involved in cluding mucous membranes The most com mon form is pemphigus vulgaris Toxic symptoms such as malaise, loss of weight, elevation of temperature and anemia are in proportion to the severity of the cutane ous involvement The disease always term inates fatally Some patients have had repeated remissions and have stayed alive for many months

Treatment

Treatment is largely symptomatic and supportive Some patients appear to im prove when the secondary pyogenic in vaders are controlled with injections of penicillin There appears to be some im provement following the administration of aureomycin Acetarsone was thought for a time to be effectual but unfortunately it is not any more valuable than other arsen icals Suramin (germanin) even though very toxic was found to be ineffectual ACTH and cortisone may result in some improvement in most cases and in some cases the remissions with the use of these hormones have lasted several years Thus so far there is nothing that is effective except ACTH and cortisone which bring about spectacular remissions in some very severe cases or may cause exacerbations even while

75 r for a total of eight times to the affected areas exclusive of the mucous membranes and one of the heavy metals Since the cause of lichen planus is unknown, the treatment is empirical but the methods described above have been found to be the most useful In some instances of chronic lichen planus nothing seems to produce a favorable response

LUPUS ERYTHEMATOSUS

Lupus erythematosus is an inflammatory dermatosis the etiology of which was thought at one time to be of tuberculous origin but is now regarded to be more frequently associated with a low grade streptococcal infection than with any other assignable cause The true etiology is seldom ascertained There are two main forms of lupus erythematosus the discoid and the acute disseminated type

The *discoid type* is characterized by the appearance of dry scaly erythematous patches which are sharply demarcated and occur most frequently on the face and sometimes arrange themselves on the nose and face simulating the appearance of a butterfly or bat wing The scales are dry and adherent and the follicles are patulous The superficial variety heals completely and leaves no scars but the deeper varieties cause marked disfigurement When hairy parts are involved, there is permanent alopecia Mucous membranes also may be affected

In the *acute disseminated variety* the clinical picture is quite different The eruption may begin suddenly quickly become generalized and resemble erythema multiforme The temperature is slightly elevated and there is leukopenia Most patients run a rapid downhill course In a few instances the generalized acute type starts with discoid lesions with gradual spreading There may or may not be a history of exposure to sunlight Patients with lupus erythematosus do not tolerate ultraviolet rays and should avoid all possible exposure

Treatment

The treatment is symptomatic, especially for the disseminated variety The general health must be maintained at an optimal level by removal of foci of infection, administration of vitamins, liver injections, and even transfusions The administration of amino acids may be helpful Iodine, sulfonamides, penicillin, *p* aminobenzoic acid, and steroid hormones appear to help in some instances ACTH and cortisone produce remissions The discoid variety is usually benefited by the administration of bismuth by intramuscular injections Gold sodium thiosulfate is also valuable Arsenic in the form of bismarsen" or ' mapharsen is beneficial The internal administration of quinine in doses of 0 3 Gm three times daily and the painting of the local areas with tincture of iodine has been of benefit in some instances White lotion, solid carbon dioxide and lactic acid are other local agents which are beneficial

The superficial variety responds to superficial roentgen ray therapy Ultraviolet light in any form and in any quantity is absolutely contraindicated in all patients with lupus erythematosus whether or not cutaneous lesions are present The acute disseminated variety with visceral lesions requires treatment depending upon the presenting symptoms Such patients should be hospitalized

Molluscum Contagiosum

The lesions of molluscum contagiosum are discrete and multiple and occur on any part of the body They are small waxy globular tumors with central slight umbilication There are not any subjective symptoms and the disease is said to be caused by a virus

The treatment consists of simple removal with a curette and painting the base with

associated with arthritis However recurrence is the rule even while under medication The side-effects and the reactions may prove to be more serious than the psoriasis So far as we know now there has never been a single case of psoriasis cured with cortisone or ACTH These drugs certainly should not be used for the treatment of ordinary psoriasis

The rind of lemon has been suggested as possessing mysterious influence over psoriasis but this claim has been disproven Sarsaparilla was used for a time but it only separates patients and their money Lecithin therapy may have some basis since there is a disturbance of cholesterol metabolism in some patients with psoriasis but in our hands this agent has been unsuccessful The same is true with special diets At one period a nitrogen free diet was advocated at another low-carbohydrate and also low fat diets Deficient diets of any type cause only temporary improvement

Topical Treatment

Psoriasis is best managed with well regulated topical remedies The best single agent is chrysarobin It is messy stains skin and clothing and is irritating to the eyes Nevertheless an ointment of 1 or 2 per cent chrysarobin well rubbed in each night after a bath will do much to clear up the lesions—especially the thickened inveterate patches Chrysarobin should not be applied to patches on the face ears or scalp For this purpose an ointment of 2 per cent salicylic acid and 6 per cent ammoniated mercury in a hydrophilic base is practical A substitute for chrysarobin which is less messy and irritating is anthralin in concentrations of 0 1–0 5 per cent

Tar and Ultraviolet Light The most common method of treating psoriasis today is by a combination of one of the tar preparations and ultraviolet light The patient is instructed to take a bath each night to soak off the scales then to apply an ointment of 3 per cent crude coal tar in petrolatum This is allowed to stay on over night and the next morning the entire body is exposed to ultraviolet rays The patient is then permitted to take a cleansing shower and put on clean clothes There are many modifications of the treatment Tar products which do not stain are used tar distillates of various types are used tar solutions are put on just prior to irradiation the source of ultraviolet may be natural sun carbon arc lamp hot or cold quartz lamp professional model or home type sun lamps or even just ultraviolet ray bulbs All of these modifications are effective in most instances The patient and the doctor use the method which is most practical and inexpensive

A few patients do not improve by any type of treatment except by changing locale and going to a resort where they may expose their entire bodies to sunshine and where they have available outdoor bathing Overexposure to ultraviolet light must be avoided otherwise psoriasis may appear where the skin has become sunburnt

Roentgen Ray Treatment Most patients with psoriasis respond very well to roentgen ray therapy There is the danger however of overexposure Expertly administered and in doses just sufficient to cause involution of the lesions roentgen ray therapy is safe The danger associated with roentgen rays stems from too frequently repeated courses of treatment and from using doses larger than are necessary A safe guide is to limit any one area to a series of four treatments given at weekly intervals in doses of 75 r of low voltage (100 Kv) unfiltered roentgen rays This course may be repeated once a year for four or five years For psoriasis of the nails the same doses of roentgen rays may be given

Psychotherapy Since many bouts of psoriasis especially the extensive cases are precipitated by emotional stress and strain it is well to advise the patient to avoid all possible tension and to practice assurance therapy We know that psoriasis is an in

under medication Blood from recovered patients has provided only disappointing results

Transfusion, liver injections high vitamin intake, high protein diet, and excessive amounts of amino acids have caused temporary improvement in some instances Potassium permanganate baths (1 10 000) relieve local symptoms and control the odor and secondary saprophytes The application of compression bandages such as are used in burn cases is the best local treatment after bathing In the absence of bandaging the free use of sterilized dusting powder (talc) may make the patient more comfortable The mouth must be rinsed frequently with warm saline solution, mild peroxide solution or diluted antiseptic liquid (N F) to which has been added 5 per cent benzocaine to control severe pain Continuous sedation and medicaments to control pain should be given

PITYRIASIS ROSEA

Pityriasis rosea is an acute dermatosis characterized by superficial pale red oval or round scaling patches with fawn colored centers The lesions are situated chiefly on the trunk and in the lines of cleavage A large herald patch simulating tinea circinata often precedes the general eruption by a week or so The etiology is unknown, and the disease self limiting usually lasting four to six weeks However, in some instances the disease is more persistent and lasts for months

There is not any specific treatment for pityriasis rosea Salicylic acid, 1 or 2 per cent in hydrophilic ointment U S P XIV can be prescribed Pruritus may be present and require the use of an antipruritic lotion or emulsion Mild desquamative or sub erythema doses of ultraviolet radiation from cold quartz type apparatus once or twice a week will hasten the involution of the lesions Caution is necessary as overtreatment may cause a severe exfoliative dermatitis

Some cases become severely eczematized through the injudicious use of medication Soothing measures such as starch baths and antipruritic lotions or emulsions should be prescribed A few fractional doses of superficial low voltage unfiltered roentgen rays are of great benefit in recalcitrant and eczematized cases

PSORIASIS

The common types of psoriasis are the guttate, nummular, and inveterate Occasionally the three types are found in the same individual It appears at any age and in both sexes and may be localized to a limited area or generalized and rarely universal in the form of dermatitis exfoliativa psoriaticum There is not a known cause for psoriasis but there is a tendency for it to be familial There are not usually any visceral complications The disease has a predilection for the tips of the elbows knees nails, scalp and ears It appears as well demarcated erythematous patches of various sizes covered with a dry mica like scale The disease may last for months or years There is not any specific treatment for the disease but with appropriate treatment it at least can be controlled

Treatment

Since there is not an ascertainable cause for psoriasis there is not any one medication taken internally that will control the disease For years arsenic in various forms has been prescribed but in many instances this medication only caused arsenical dermatitis and arsenical keratoses It should not be used Recently sodium undecylenate has been recommended but clinical trial on thousands of cases has shown this drug to be absolutely useless

Cortisone and ACTH causes psoriasis to involute sometimes, especially if the psoriasis is of the severe and extensive type and is

treatment of pruritus ani and results in a high percentage of cures Ultraviolet radiation is less helpful However, painting the area with coal tar solution prior to exposure to ultraviolet rays enhances the therapeutic result

Other measures including tattooing with mercury sulfide, alcohol injections, or nerve resection have been proposed in stubborn cases Proper dermatologic management appears to be equally if not more effective

Systemic treatment includes the control of constipation by an appropriate diet and the use of mild cathartics or mineral oil to minimize trauma at stool Where neurogenic factors are pronounced an attempt should be made to readjust the patient to his environment If this is not possible a vacation at a health resort or spa may result in gratifying improvement or cure Antihistaminic drugs and/or sedatives may be helpful and should be given a trial

Pruritus Vulvae

Pruritus vulvae usually occurs after the menopause but it is not uncommon in younger women Neurogenic factors are also paramount in this form of pruritus However, other factors such as monilia infection, trichomonas vaginalis hormonal changes, local pathology due to kraurosis vulvae or leukoplakia, leukorrhea, or contact dermatitis from douches, contraceptive material or medication may be significant In general, the topical and systemic treatment of pruritus ani applies equally to pruritus vulvae Hormonal therapy with diethylstilbestrol, estradiol or other estrogens may be indicated in the presence of the menopause

Senile Pruritus

Senile pruritus occurs in the aged and is usually generalized It is due to the atrophic and degenerative changes of the skin incident to aging However, all possible causes of generalized pruritus such as diabetes mellitus, latent jaundice, hepatic disease blood dyscrasia, lymphoblastoma, visceral carcinoma, uremia, and drug ingestion must be excluded before senile pruritus can be diagnosed

Treatment consists of relatively simple measures directed toward the prevention of friction and drying of the skin The use of soap is kept at a minimum If the patient is unimproved, synthetic detergents such as Lowila or Acidolate are advisable Less frequent bathing is encouraged and one cup each of starch and sodium bicarbonate may be added to the bath water Long cotton underwear is worn to avoid friction from wool clothing

Hydrophilic ointment, either plain or containing 1 per cent phenol, may be applied to the affected areas to ameliorate itching and provide lubrication Vitamin A 50 000–100,000 units daily may be beneficial Ultraviolet radiation with the hot quartz lamp in short exposures is sometimes of value Patients who do not respond favorably to this regimen may become irritable, fatigued, or depressed A vacation at a health resort or spa with its well regulated life and with facilities for medicated baths, steaming, massage, etc, should provide much relief to the patient The use of antihistaminics may allay the severe itching

RADIODERMATITIS

Excessive exposure of the skin to roentgen rays, grenz rays, radium radioactive isotopes radon ointment, thorium X or any ionizing radiation results in a roentgen ray burn There are two types of radiodermatitis, acute and chronic

The *acute* type is divided into three degrees, first, second, and third The first degree is simple erythema, the second degree is characterized by vesicle formation and the third degree by ulceration The ulcers are extremely painful The severity of the burn is directly proportional to the amount of radiation—usually at a single

curable disease, and is it not far better to assure the patient that much can be done to control the presenting attack? We know of patients who had extensive psoriasis but who have remained well without treatment for over twenty years

Arthritis

The association of psoriasis with arthritis is well recognized When this is the case, treatment with ACTH or cortisone has been effective Both the psoriasis and the arthritis are ameliorated by such treatment In many instances, however, improvement persists as long as the treatment is continued The dose of cortisone for the first day is 0 2–0 3 Gm and is decreased to a maintenance level as soon as improvement is noted The two diseases require individual treatment One danger to be avoided is irradiation with ultraviolet light of the whole or part of the body while the patient is receiving gold therapy for the arthritis Gold is a photosensitizing drug and severe complications may result from the combined method of treatment

PRURITUS (ANI, VULVAE, AND SENILIS)

Pruritus Ani

Pruritus ani is a relatively common condition which occurs chiefly in men In women it is frequently associated with pruritus vulvae Excoriations fissures lichenification, and frequently a superimposed contact dermatitis are common local findings In most individuals anxiety, tension and emotional stress and strain appear to play a dominant etiologic role in the production of the disease However numerous other causes may account for pruritus ani and must be investigated before therapy is undertaken These include bacterial or mycotic infection intestinal parasitic infestation, localized atopic dermatitis, contact dermatitis seborrheic dermatitis, psoriasis, diabetes mellitus, constipation, intestinal or visceral neoplasms, and local anal or rectal pathologic lesions An exceedingly important contributory factor is local maceration and irritation due to sweating and lack of proper local hygiene A thorough physical examination including a rectal digital examination and a stool analysis is desirable before undertaking treatment Mycologic and bacteriologic studies also may be in order

Treatment

In the absence of specific findings which would be treated appropriately, symptomatic treatment is undertaken The patient is instructed in proper rectal hygiene Friction is avoided in postdefecation cleansing by the use of absorbent cotton or soft toilet tissue moistened with mineral oil, water, or boric acid solution Frequent sitz baths are exceedingly helpful in eczematized and severely pruritic cases One cup of starch or 5 cc. potassium permanganate crystals are dissolved in one half tub lukewarm water for the sitz bath

Local Treatment The choice of local medicaments depends on the process When acute and exudative, wet dressings are indicated A soothing preparation such as the zinc oxide paste may be used between applications of wet dressings In the subacute or chronic stage with infiltration and lichenification of the skin 3–6 per cent coal tar solution or 3–5 per cent coal tar may be added to the above ointments A relatively safe antipruritic agent may be made by adding 1 per cent phenol to these preparations Some topical anesthetic agents however, have a relatively high sensitizing index and must be employed with caution Antihistaminic ointments are sometimes effective in controlling pruritus even of long duration, but are sensitizing Fissures are painted with 2 per cent silver nitrate or copper sulfate solution, or 2 per cent aqueous solution of gentian violet

Roentgen therapy given in doses of 75 r once a week for a total of four treatments is one of the most useful agents in the

such as skolex' and "A fil' Another preparation may be compounded as follows

	Per cent
Phenyl salicylate	2
Tannic acid	6
Diluted alcohol sufficient quantity	

VERRUCAE

Verrucae or warts may occur in several forms They are autoinoculable probably contagious, and due to a virus

Verruca vulgaris is the common wart It usually occurs on the fingers and backs of the hands but may occur on any part of the body Verruca plantaris appears on the sole and usually is painful Verruca plana juvenilis occurs chiefly on the face neck and dorsum of the hands the lesions are smooth flat and slightly elevated varying from a pinhead to small split pea-sized It is more common in children Verruca acuminata or venereal warts consist of papillary growths of filiform projections and are found usually on the genitalia perineum or anus They are not due to venereal infection

Verruca Vulgaris

Verruca vulgaris may be destroyed by several applications of a caustic agent such as trichloracetic acid or dichloracetic acid or by refrigeration with solid carbon dioxide A better result is assured, however, when the lesion is infiltrated with procaine hydrochloride solution 1-2 per cent, and electrodesiccation and currettage are performed Roentgen rays are highly successful but must be administered by an expert in their use Intramuscular injections of bismuth at weekly intervals may produce disappearance of the lesions A wart vaccine is used by some but the method is impracticable and prolonged The efficacy of such treatment has not been proven

Verruca Plantaris

Verruca plantaris responds favorably in most cases to therapy with roentgen rays Surgical excision or curettage and cauterization with heat or acid, or removal by electrodesiccation and curettage are effective, but usually result in temporary but painful disability Repeated paring and the application of 40 per cent salicylic acid plaster is laborious and slow to effect a cure Since orthopedic defects are frequently the predisposing cause in the production of verruca plantaris the services of an orthopedic specialist for their correction is essential to prevent recurrences Systemic therapy with bismuth is usually ineffective The most practical approach for the treatment of a single painful wart on the sole is destruction of the lesion, under procaine anesthesia with an electrosurgical current the charred debris is removed with a curette and after the entire wart has been removed the base is electrodesiccated The resulting wound is protected with chiropodist's felt and treated as a slow healing wound

Verruca Plana Juvenilis Verruca plana juvenilis may be cured by the same measures employed for verruca vulgaris However the lesions are usually so numerous that systemic therapy with mercury protiodide (yellow mercurous iodide tablets N F) 6-10 mg three times daily, is first attempted A cure usually results in children within a few months but it is less successful in adults Painting with Vleminckx's solution daily is occasionally successful Roentgen rays sometimes produce involution of the lesions after several doses of 75 r of low voltage unfiltered roentgen rays Suggestion therapy is reputed to yield surprising results in some cases in both the juvenile and common warts Those that persist after conservative therapy has been tried have to be treated with the mild electrodesiccating current

Verruca Acuminata Verruca acuminata is best treated with podophyllin resin 25 per cent in mineral oil or ointment base or 20 per cent in alcohol The alcoholic preparation appears to be less irritating to the

sitting or in several exposures at short intervals

The *chronic* type usually results from many small treatments over a period of months or years Skin changes occur years after cessation of radiation The chronic type is characterized by atrophy, telangiectasia pigmentation and in more advanced cases keratoses and even epithelioma formation

Treatment

Treatment depends upon the type and stage The acute erythema does not require special treatment except the application of bland preparations such as boric acid compresses during the daytime and cold cream or petrolatum at night The ulcerative forms whether of the acute or chronic variety are best treated by excision These ulcers are so painful that patients welcome the relief which surgery affords them Radon and thorium X ointments have been advocated but it seems illogical to apply more ionizing radiations to tissue which has been destroyed by ionizing radiations

The late manifestations of radiodermatitis need not be treated except to avoid trauma irritants and more radiations An exception is management of keratoses and the epitheliomas All epitheliomas should be destroyed as soon as they appear either by excision or by electrosurgical destruction they should not be treated with roentgen rays or radium even though they respond to these agents By destroying all keratoses early cancer developing in radiodermatitis may be avoided When cutaneous malignancies do develop in radiodermatitis they should be destroyed immediately by electrosurgery or by excision

For years the actual leaf from the plant *Aloe vera* was used with some success in some of the manifestations of radiodermatitis especially the ulcers More recently a jelly made from the leaf has been used by some dermatologists The beneficial results from this type of treatment is questionable Vitamin A & D ointment seems to be of some value in ulcers from overexposure to roentgen rays Equally beneficial are other antibiotic ointments because they control secondary infections All these are temporary measures and the results are always uncertain Nothing can substitute for clean cut extirpation when feasible A patient with radiodermatitis must be kept constantly under the watchful eye of a trained dermatologist lest the disease progress to cancer

SUNBURN

Sunburn is classified similarly to other burns as first second or third degree Extensive burns of the second and third degree varieties require hospitalization expert nursing sedation pressure dressings hematocrit studies, plasma transfusions, and other appropriate treatment

The treatment is that for any acute dermatitis When edema erythema or vesiculation are present wet dressings of normal saline or boric acid should be employed Starch and sodium bicarbonate baths are soothing Sedatives or analgesics may be necessary Petrolatum boric acid ointment or a soothing emulsion such as lime liniment (carron oil) are suitable when exudation is absent or has subsided The use of antibiotics and/or sulfonamides may be indicated if secondary infection is a complication

To prevent sunburn certain preparations are recommended The patient is instructed to apply the ointment or lotion prior to exposure to the sun Patients with lupus erythematosus or with xeroderma pigmentosum or those with other light sensitive diseases are advised to use liberal quantities of one of the medicaments before sun exposure Fifteen per cent *p* aminobenzoic acid in hydrophilic ointment (U.S P XIV) or sun cream (N F VIII) are satisfactory There are many proprietary preparations

of natural Tuberculin injections helped slightly The best treatment is with calciferol (vitamin D_2) in doses of 200 000 to 300 000 units per day However one must watch carefully for evidence of a rise in serum calcium and for calcification in kidneys and vessel walls Roentgen ray therapy is occasionally beneficial and small lesions may be excised or destroyed with electro surgery *or with strong chemicals* The general health has to be watched carefully Fresh air sunshine ample and nourishing food and adequate rest are essential adjuvants In some stubborn cases the use of streptomycin along with calciferol yields better results than either employed alone Antibiotic ointments applied to ulcerated areas are *helpful* The newer compounds of nicotinic acid such as isonicotinic acid hydrazide (isoniazide) may prove valuable in all forms of tuberculosis affecting the skin The early reports are certainly encouraging

SCROFULODERMA

This form of skin tuberculosis is fast disappearing from this country This is because of the universal practice of pasteurizing milk and the careful watch of health authorities over cattle and dairy farmers Ulcerations secondary to involvement of cervical lymph nodes are the most common manifestations

This variety of skin tuberculosis also *responds well to vitamin D Generalized* and localized ultraviolet ray therapy is valuable Nodes which are definitely fluctuant must be incised and drained if the area is small it may be advisable to excise the entire mass Penicillin may be of value to control secondary infections Streptomycin has not been particularly successful and *is not an entirely safe* drug to use

PAPULONECROTIC TUBERCULID

The usual sites of predilection of papulonecrotic tuberculid are the face and the extremities The lesions are discrete and are in all stages of evolution and involution from a papule to a small ulcerated area They are probably caused by showers of attenuated tubercle bacilli This affection is rather common and is occasionally associated with erythema induratum of Bazin

The treatment of papulonecrotic tuberculid is both local and general To control the secondary infection tyrothricin bacitracin or ammoniated mercury ointment is used Vitamin D_2 in doses of 100 000 to 200 000 units per day is valuable Also helpful is generalized and localized ultraviolet radiation Bed rest is not necessary but measures to improve the general health are definitely indicated

ERYTHEMA INDURATUM

Bazin s disease is in some respects similar to papulonecrotic tuberculid except that the lower extremities particularly the calves of young women whose occupations require them to stand for long periods are involved In patients so affected there is usually a history of exposure to tuberculosis

The treatment of this condition in a general way is similar to that for papulonecrotic tuberculid except that the deep ulcers of the legs respond better and quicker with bed rest compression bandaging and elevation of the extremities The combination of tuberculin injections generalized and localized ultraviolet light and supportive dressings of the extremities is particularly effectual Antibiotic ointments and the internal use of calciferol are useful

ERYTHEMA NODOSUM

This disease is not always caused by the tubercle bacillus It is a cutaneous manifestation secondary to a toxic or bacterial process It most commonly is found associated with severe illnesses such as toxemia of pregnancy and endocarditis It is manifested by the sudden appearance of large painful subcutaneous nodules

normal mucosa It is applied to the affected area after the normal tissue is protected with mineral oil or petrolatum In several hours the area is washed to remove any remaining podophyllin The lesions usually disappear within a few days If they are not entirely gone the treatment may be repeated and the application permitted to remain on longer Electrodesiccation is now reserved for the few failures Roentgen radiations are never used for this type of lesions

CLAVUS

Corns are hypertrophic lesions of the horny layer of the epidermis which are too familiar to require further description Hard corns are usually present on the feet in an area of pressure from footgear or from some orthopedic abnormality When they appear in other locations such as the palms and fingers the cause is usually occupational Soft corns occur in the interdigital spaces of the toes from lateral pressure and from the maceration incident to perspiration

The elimination of pressure will frequently cause spontaneous involution Pain can be relieved by the use of chiropodist felt pads with a central opening and by the use of warm magnesium sulfate or boric acid soaks Paring periodically with the scalpel and the application of keratolytic medicaments as 10–40 per cent salicylic acid plaster, or 20 per cent salicylic acid in collodion will effect a more rapid resolution of the hypertrophic lesion Proper footgear and orthopedic correction are necessary to prevent recurrence

VINCENT S ANGINA

This is an acute ulcerative infection involving usually the mouth but it may be seen on the skin and the penis It is caused by Vincent s organisms (fusiform bacilli and spirochetes) The ulcerations in trench mouth are painful and deep and they progress if not treated The lymph nodes are generally involved, and eating and swallowing are difficult *

The disease responds exceptionally well to the local and intramuscular use of penicillin One to several daily doses of 300 000 units of penicillin is sufficient to cure the average patient Penicillin lozenges of 5000 units each or aureomycin troches are helpful as are sprayings with a solution containing 250–500 units of penicillin per cc In some cases it is necessary to supplement this treatment with frequent washing of the mouth with sodium perborate Arsphenamine and later neo arsphenamine and mapharsen' were used intravenously and locally These agents are not used now because the antibiotics are effective

* See also Chapter 36

Tuberculodermas

LUPUS VULGARIS

Lupus vulgaris is the most prevalent form of tuberculosis of the skin It usually starts early in life on the face and spreads exceedingly slowly except in those individuals whose susceptibility is unusually high to the tubercle bacillus Some have estimated that pulmonary tuberculosis is present in about 25 per cent of patients with lupus vulgaris The so-called apple jelly nodule is almost a constant finding in lesions of lupus vulgaris Most patients with lupus vulgaris living in the United States are in good general health

The treatment of lupus vulgaris was very discouraging until very recently The only effective treatment was prolonged use of ultraviolet light, either artificial (Finsen)

obvious The depth dose may injure important underlying structures

Since many hemangiomas undergo spontaneous involution often there is a question of treatment However spontaneous involution may be accompanied by ulceration hemorrhage secondary infection and unsightly scarring Thus skillful treatment will yield better cosmetic results It should be undertaken as early as possible in infancy since the tumor is more radiosensitive and more amenable to therapy at this time It is a mistake to wait until the infant is a year or older In deep cavernous lesions disfiguring bony involvement may be marked if treatment is delayed A patient with a hemangioma *should be* treated as soon as possible to produce optimum cosmetic results

PORT-WINE STAINS

The port wine stain port wine mark or nevus flammeus presents a problem quite different from that of angiomas above This *form of birthmark is flat pink to deep* purple and involves small or very large areas of the body The color becomes more intense on crying or coughing Faint lesions may undergo spontaneous resolution but ordinarily the lesion persists throughout life

There is not an entirely satisfactory treatment of port wine stains Roentgen rays radium ultraviolet rays in caustic doses from the Kromayer lamp electrodesiccation and refrigeration have been used *but the results are uniformly poor* Overtreatment with radium or roentgen rays causes radiodermatitis Treatment with these agents must be intensive to effect any change in the lesion The result is less satisfactory and more disfiguring than the original lesion which can be disguised easily Covermark or pancake makeup very effectively masks the untreated lesion Moreover dangerous sequelae may follow the injudicious use of roentgen rays or radium Grenz rays and thorium X are reported by some observers to give favorable results but this has not been corroborated by our experience or by that of many other dermatologists although one of these agents (thorium X) has been used for thirty five years and the other (grenz rays) for over twenty years Tattooing with carefully selected *pigments and sliding graft* operations offer promise for the future

NEVUS PIGMENTOSUS ET PILOSUS

Nevus pigmentosus et pilosus is an intradermal nevus and rarely if ever undergoes malignant degeneration The lesion may be present at birth or soon after birth *It may* involve small or huge portions of the body and at any site The color varies from light to dark brown The surface may be relatively smooth but is often rough and verrucous The lesion may be flat or slightly elevated The hairs may be fine or coarse sparse, or numerous

Despite the benign course of these lesions it is advisable to remove them when they are present in an area subjected to repeated trauma such as the belt line or the bearded region Frequently treatment is requested for cosmetic reasons

Removal of the hairs in small lesions by electrolysis usually causes diminution in the size of the lesion and of the intensity of pigmentation Further treatment may not be required In most cases it is necessary to produce further depigmentation of the lesion *by lightly freezing it with solid carbon* dioxide at intervals of three to four weeks Electrodesiccation at one sitting or fractionally at monthly intervals or surgical excision may be the method of choice depending on the size and site of the nevus For extensive lesions reparative surgery or no treatment may be advisable Experience is required in the exercise of any of the above modalities to effect a satisfactory cosmetic result

Treatment consists of finding and eliminating the cause The treatment of the underlying condition is of paramount importance When the eruption is due to a drug the responsible medicament must be discontinued The sulfonamides and the antibiotics are indicated in instances when there is severe systemic infection

SARCOID

Sarcoidosis is a systemic disease with cutaneous and visceral involvement especially of the lungs, tonsils lymphoid tissues and bones There are two main varieties occurring on the skin the superficial and deep The cause of sarcoidosis has not been established

In the treatment of sarcoid arsenic cortisone ACTH and roentgen rays have been found to be the most effectual agents Calciferol has been used by some with good results Streptomycin has not been used sufficiently to permit evaluation of its usefulness Injections of chaulmoogra oil and tuberculin have been recommended In most cases the disease runs a definite course and there appears to be spontaneous healing The patients do not show signs of toxicity even when the disease is extensive

Congenital Abnormalities

HEMANGIOMA

Hemangiomas are vascular nevi and consist of groups of blood vessels and sinuses They are present at birth or appear within the first few weeks of life The lesions may be superficial or deep

ANGIOMA SIMPLEX

Angioma simplex or strawberry mark is the superficial type and is commonly found on the face scalp, shoulder or buttocks but may appear at any site The lesion is bright red elevated somewhat lobulated like a strawberry and easily recognized Skillful freezing of the strawberry mark with solid carbon dioxide will effect an excellent cosmetic result Moderate pressure is used for five to ten seconds until the area is completely blanched and frozen The procedure is repeated at intervals of three to four weeks until the lesion is flat and pale The number of treatments depends on the depth and extent of the lesion Beta rays of radium are more rapidly effective but this agent is not as easily obtained as commercial dry ice A single suberythema dose may be sufficient to cause involution

Cavernous Angioma

Cavernous angiomas are deep vascular nevi The lesion is usually a circumscribed mass covered by normal epidermis to which a bluish color has been imparted by the underlying blood vessels or the surface may be similar to that of a strawberry mark The lesion may or may not be elevated appreciably Cavernous angiomata respond to refrigeration with solid carbon dioxide but other methods are preferred The injection of sclerosing solutions in large angiomas is an excellent method of treatment and produces good cosmetic results Surgical extirpation of the lesion may be performed providing the site of the lesion and the size are suitable but this method is not used widely The treatment of choice is the use of gamma rays of radium at a distance chosen to furnish the appropriate depth dose for the tumor The depth of the lesion is the determining factor The source of radiation may be tubes needles or plaques but appropriate filtration is required to provide gamma radiation Roentgen rays also are effective but the difficulty of irradiating a restless infant is

tonite 10 per cent and 3-5 per cent tannic acid may be added

Dermatophytosis or intertriginous dermatitis may accompany hyperidrosis and require treatment

BROMIDROSIS

Bromidrosis or malodorous sweating may be associated with hyperidrosis or occur independently It may be generalized (rarely) or localized Causes may include certain drugs as valerian or asafetida or foods as onions or garlic decomposition of retained sweat in intertriginous areas or poor hygiene Bromidrosis of the feet, axillae inframammary and anogenital regions is the usual form of localized involvement

The treatment of bromidrosis is quite similar to that outlined for hyperidrosis Recently chlorophyll taken by mouth has been advocated as an effective method for overcoming undesirable body odors Banthine also controls bromidrosis Personal cleanliness frequent bathing and changes of clothing are essential Local therapy consists of the use of potassium permanganate soaks and a deodorant and antiperspirant lotion or powder Those described for the treatment of hyperidrosis are suitable Perfume may be added

Treatment with roentgen rays is effectual for both hyperidrosis and bromidrosis It is the only way of permanently eradicating the disease However this form of therapy should not be used routinely because the dose required to produce favorable results is so near the toleration dose that there is always danger of overirradiation and the development of radiodermatitis months or years after the roentgen rays have been administered Grenz rays are ineffectual and are not any safer Roentgen therapy should be reserved for the most severe and uncontrollable cases

HYPERTRICHOSIS

The common type of hypertrichosis or superfluous hair in women usually affects the lip or chin but may involve the entire bearded region It may appear at the onset of puberty or at a later period Pregnancy and the menopause are sometimes marked by increased hair growth Pituitary adrenal or ovarian tumors may cause hirsutism as well as other distinctive changes and must be excluded by thorough examination The majority of patients with hypertrichosis of the face however, are in good health and do not present any patent abnormalities

Hypertrichosis due to an endocrine disorder or to a tumor requires appropriate medical or surgical treatment The common type of hypertrichosis unattended by any abnormalities may be controlled in a variety of ways The use of high frequency currents for depilation is the most satisfactory and rapid method of permanently removing superfluous hair safely The procedure is slightly painful Electrolysis with galvanic current is equally good but fewer hairs can be removed at each treatment Depilatory waxes or chemicals as barium sulfide are commercially available and are effective although temporary measures for the removal of hair Abrasives as pumice stone and sandpaper mittens wear off the protruding hairs So far as is known this does not have any effect on subsequent growth Plucking or cutting the hairs or even shaving may be preferred by some patients There is not any evidence to show that any of these measures increase hair growth Bleaching with mild ammonia water and hydrogen peroxide is often satisfactory for masking fine hairs

The use of roentgen rays radium or devices which emit ionizing radiation for the permanent removal of unwanted hair cannot be condemned too severely It is impossible to effect this result without producing sequelae which may give rise to squamous cell carcinoma Every successful depilation with roentgen rays is always followed by radiodermatitis months or years later even though the immediate result appears to be excellent

ICHTHYOSIS

Ichthyosis simplex or ichthyosis vulgaris or fish skin disease is a congenital disorder characterized by the presence of dry, quadrilateral or diamond shaped scales on the extensor surfaces of the arms and legs In severe cases the flexors may also be involved A mild form of the disease known as xeroderma is manifested by dryness of the skin of the extensor surfaces of the arms and legs with furfuraceous scaling and associated keratosis pilaris The nails are brittle and easily broken The hair becomes excessively dry and body secretions are diminished Exacerbations are marked during cold weather

The treatment of ichthyosis vulgaris is symptomatic There is not a cure for the disease Dryness is counteracted by the frequent application of a bland oil, grease, or ointment olive or mineral oil cocoa butter, petrolatum lanolin and other preparations are beneficial An effective preparation is an ointment of equal parts of theobroma oil, petrolatum, and hydrous wool fat

When pruritus is a feature of the condition one per cent phenol or 0 1 per cent menthol may be added to the preparation Baths of starch, bran or oatmeal are soothing Soap should be used sparingly and a synthetic detergent or superfatted product preferred Warm clothing minimizes symptoms especially in winter Vitamin A in doses of 100 000 units or more daily, orally and parenterally has been followed by some relief

Diseases of the Appendages

HYPERIDROSIS

Hyperidrosis or excessive sweating may be of physiologic or pathologic origin Physiologic hyperidrosis may be due to elevated temperature of the environment muscular exertion ingestion of hot drinks or food alcohol or drugs Pathologic hyperidrosis may be associated with systemic diseases such as hyperthyroidism tuberculosis malaria anemia or organic disease of the central nervous system However pathologic hyperidrosis is usually local rather than generalized

The causes of local hyperidrosis are frequently obscure although the sympathetic nervous system apparently plays an important role Many of the individuals who suffer from localized hyperidrosis are emotionally unstable and the victims of vasomotor instability* The hands feet, genitals axillae and face are usually involved These parts of the body may be cold and cyanotic

The treatment of physiologic hyperidrosis is too obvious to require any elaboration Generalized pathologic hyperidrosis demands treatment of the underlying condition Sponging bathing application of cooling powders such as talc containing 0 1 per cent menthol and other suitable measures will make these patients more comfortable The use of belladonna banthine or atropine to inhibit perspiration is rarely indicated

Localized hyperidrosis requires attention to the general health of the neurasthenic individual and the employment of local measures Aluminum chloride, 10–25 per cent in distilled water, is an effective antiperspirant It may be applied daily if tolerated Bathing the affected areas daily in a solution of potassium permanganate (1 6000) or sponging with a weak solution of formalin (1 per cent alcoholic) is effective Talc containing 1–2 per cent salicylic acid and 5 per cent boric acid is of benefit as a dusting powder Ben

of stinging This occurs within a few seconds The procedure is repeated at intervals of two to four weeks It produces erythema followed by scaling Ultraviolet rays may be used to produce erythema instead of the *phenol* A *stimulating lotion* as one of those prescribed for alopecia seborrheica is also appropriate

There is not any evidence to substantiate the claims made by some that roentgen rays, grenz rays, and other radioactive agents such as thorium X will cause hair to grow in cases of alopecia areata In fact such treatment may be definitely harmful and therefore should not be used indiscriminately

ACTH and Cortisone

SINCE cortisone and ACTH are new drugs, a summary of their use in dermatology may be of help to some physicians They should not be used indiscriminately

Cortisone and ACTH have been used extensively *for the treatment of skin diseases* In some cases use has been extremely beneficial, in other cases it has not helped the condition for which prescribed and in other cases the side effects and the reactions which resulted from the administration of these two drugs were worse than the disease for which they were prescribed Some physicians have prescribed these two hormones with the idea that the condition would be cured At one time or another the following diseases have been treated with cortisone and ACTH alopecia areata atopic eczema chronic generalized eczema chronic discoid lichenoid and exudative dermatitis chronic urticaria from penicillin and other drugs dermatomyositis dermatitis herpetiformis dermatitis venenata *epidermolysis bullosa erythema* bullosum malignum erythema multiforme erythroderma desquamativa exfoliative dermatitis, generalized neurodermatitis hypostatic eczema Kaposi s sarcoma, keloids lupus erythematosus both chronic discoid and acute disseminated nutritional eczema (pellagra like) pemphigus periarteritis nodosa pruritus vulvae, senilis, and ani psoriasis (with and without arthritis) sarcoid scleroderma, seborrheic dermatitis

We have learned by experience that the hormones are of limited usefulness in *dermatology They should be used* conservatively, and only after conventional measures have failed to bring about the desired result When properly used in conditions where one expects to obtain favorable results the hormones have proven to be invaluable therapeutic agents

There is no dosage schedule for these two drugs With ACTH a good initial response usually is obtained with 0 1 Gm daily in divided doses of 25 mg administered every six hours The initial dose of cortisone should be 0 2–0 3 Gm in doses of 50–100 mg administered every four to eight hours Cortisone can be used either orally or parenterally As soon as a therapeutic response is obtained then the dosage is lowered to a maintenance dose which may be anywhere from 25 to 50 per cent of the initial dose

A patient should not be kept on the *hormones indefinitely* If a quick response to treatment is not elicited within two or three days then it is well to stop the treatment

ALOPECIA

Alopecia Prematura

Alopecia prematura is a form of baldness occurring in young individuals It may be idiopathic or symptomatic Idiopathic alopecia is common in many families and is evident by a predisposition to premature loss of hair in the male independent of any local or systemic disease Other factors in the production of this type of baldness are unknown Symptomatic alopecia prematura may follow febrile diseases such as typhoid or other diseases as tuberculosis, leprosy and myxedema or debilitating diseases Exposure to sun and salt water bathing or bathing in pools does not cause extensive loss of hair *In fact, sun is beneficial*

Alopecia Seborrheica

Alopecia seborrheica is probably the most common form of alopecia Hair loss is secondary to seborrhea of the scalp Alopecia senilis usually occurs in men of advancing years and less frequently in women It is attributed to atrophic changes in the skin but seborrhea may also be a contributory factor

Predisposing causes local or systemic must be remedied by appropriate means, if possible Thyroid may be indicated In most instances the only indication is for local stimulating treatment

The patient is instructed to shampoo the scalp once or twice a week or more depending on the degree of seborrhea An ointment containing 2 per cent salicylic acid and 6 per cent precipitated sulfur or ammoniated mercury in hydrophilic ointment may be massaged into the entire scalp the night prior to shampooing There are many excellent shampoos on the market An excellent new preparation for seborrhea is selsun suspension (selenium disulfide)

In all cases of alopecia a stimulating lotion as the following should be applied to the entire scalp nightly and massaged in for several minutes For example

For dark hair	Gm or cc
Resorcinol	4–8
Betanaphthol	2–4
Mercury bichloride	0 12
Alcohol	90
Rose Water	to make 240

Label Mix Filter through talc

For light hair	
Capsicum tincture	0 6
Cantharides tincture	8–16
Formic acid spirit	4–8
Mercury bichloride	0 2
Alcohol	90
Rose water	to make 240

Label Mix Filter through talc.

Castor oil, 15 cc may be added to either of the above formulas to counteract excessive dryness

Mechanical stimulation by gentle daily brushing massage by hand or by electrical vibrator may be helpful

Alopecia Areata

Alopecia areata is characterized by the loss of hair in circumscribed areas unaccompanied by subjective symptoms or inflammation Exclamation point hairs may be seen in the affected areas The cause is unknown although many theories have been suggested It is now believed to be of neurogenic origin The lesions are usually confined to the scalp and may be single or multiple Occasionally the beard or other hairy regions of the body are involved Universal alopecia is an infrequent but distressing complication of the disease and a source of great anxiety to the patient

The prognosis of alopecia areata is almost invariably favorable although it should be guarded in cases of universal alopecia While foci of infection should be eradicated and a thorough physical examination including endocrine evaluation undertaken, these measures will usually yield little benefit.

Local stimulation is the more practical and more useful approach The patch of alopecia is painted lightly with a cotton swab moistened with liquefied phenol and neutralized with alcohol as soon as the area begins to blanch or the patient complains

Interpretation of Serologic Tests and Spinal Fluid Reports

TESTS ON THE BLOOD*

The physician must correlate the laboratory report with the history and clinical findings to reach a conclusion concerning the presence or absence of syphilis or the significance of the test in a treated patient The diagnostic tests for syphilis in current use rest upon the fact that an antibody like globulin, reagin, has the property of combining with finely divided particles of mammalian tissue lipoids (antigen), causing them to adhere and to form visible aggregates as in the various flocculation tests for syphilis (*Eagle, Hinton, Kline, Kahn, Mazzini, Venereal Disease Research Laboratory*), or to fix complement as in the Wassermann test Thus there are only two types of tests flocculation and complement fixation, to which the names of various serologists have been attached as modifications were developed The cardiolipin test is identical in principle with all other flocculation tests except that it employs a purified cardiolipin lecithin antigen, rather than beef heart lipoid

A "positive report, whether with a complement fixation or any of the flocculation tests, implies that in the opinion of the laboratory there was no doubt as to the presence of reagin in the blood specimen submitted A "doubtful' report implies that the result of the test was in doubt, including all results which were formerly reported as one plus, two plus, or three plus' A report of 'negative' indicates the failure of the particular test or tests employed to detect reagin in the particular serum sample submitted A negative serum reaction can not be accepted as absolute proof of the absence of syphilitic infection

* See also Chapter 48

False Positive Reactions

Unfortunately many factors other than syphilis may cause a false positive or false doubtful reaction Technical error is by no means infrequent even in a well-organized laboratory This may be due to mislabeling of a blood specimen or to technical maladjustment of the reagents A single positive or doubtful report, therefore, never should be accepted at face value in the absence of definite clinical findings until a confirmatory specimen is sent to the same or another laboratory The physician can utilize a laboratory approved by the state health department to minimize technical false positive or false negative reports

Reactions Due to Diseases Other than Syphilis So-called biologic false positive reactions fall into two groups those due to disease conditions other than syphilis and those occurring in otherwise apparently normal persons The literature contains a large and growing list of conditions other than syphilis which may produce false positive serologic tests False positive reactions are frequent and indubitable in leprosy acute malaria infectious mononucleosis smallpox vaccination, rat bite fever due to *Spirillum minus*, relapsing fever, disseminated lupus erythematosus, upper respiratory infections, and primary atypical pneumonia They also occur but with lesser frequency in lymphogranuloma venereum chancroid, and Haverhill fever

It is likely that the ability of many common febrile acute infections to lead to transient false positive reactions has been grossly underestimated Yaws and pinta treponemal diseases uniformly produce positive serologic tests for syphilis A partial list of other conditions which have been reported to produce false positive reactions includes repeated blood donations battle

39. *Syphilis*

RICHARD D. HAHN
& JOSEPH EARLE MOORE

Biology of Syphilitic Infection and Treatment

SYPHILITIC infection usually occurs following contact with moist surfaces oral or genital, of a recently infected individual Within a short time after exposure, probably twenty four to forty eight hours, the treponemes undergo generalized dissemination throughout the body Long before the primary lesion appears, the disease is already generalized, indicating the futility of local excision of a lesion Concomitant with this generalized spread of organisms there usually occurs multiplication at the site of inoculation resulting after an average incubation period of three weeks in the chancre About six weeks after the chancre appears, secondary lesions become visible, notably in the skin mucous membrane, eye, and nervous system because of local proliferation of the treponeme in these apparently especially susceptible structures The lesions of early syphilis, however, may be trivial and escape the attention of patient and physician Not infrequently, entirely symptomless infection may occur Primary and secondary lesions are characterized by the presence of numerous organisms with little destruction of tissue

After the healing of the secondary lesions a series of infectious relapses may follow, especially during the first two years of infection These may never appear, or, if they do sooner or later cease to occur The patient then enters a period of latency which may endure from a few months to a life time If late lesions occur, they may be of two types a violent, inflammatory reaction with marked tissue destruction, or a chronic, slowly progressive, predominantly perivascular inflammation and fibrosis usually affecting the cardiovascular or central nervous system Although the blood in late syphilis is usually assumed to be noninfectious, the occurrence of at least transient spirochetemia is indubitable as evidenced by transmission of the disease to the fetus in utero by the pregnant woman in any stage of the infection

Criteria of a False Positive Reaction Although it is true that a biologic false positive reaction is difficult to recognize on *serologic grounds alone* and that the entire clinical picture must be taken into consideration, certain serologic phenomena do suggest a false positive reaction These include (1) A persistent paradoxical serum reaction in which the more sensitive tests, particularly the cardiolipin test, are negative, and the less sensitive tests are positive (2) A negative Nelson treponemal immobilization test The Nelson test, which is no longer in the experimental stage, shows great promise It is currently being run at the Johns Hopkins School of Hygiene and Public Health, at the Naval Medical Center in Bethesda, Maryland, and at the U S Public Health Service Research Laboratory in Atlanta, Georgia

Quantitative Serologic Tests

Quantitative serologic tests for syphilis are of value in certain circumstances* Reagin ' titer is the highest dilution of serum which still gives a positive serologic test for syphilis Thus a titer of 128 means that the particular serum sample diluted with saline 128 times still gives a positive serologic test for syphilis A serum which is positive only when undiluted has a titer of 1 unit The sole exception is the Kahn unit, because Kahn has assigned a titer of 4 to undiluted positive serum, and with *the Kahn test dilu*tions are reported in multiples of four units Thus a titer of 16 with the Kahn is roughly equivalent to a titer of 4 with other flocculation tests In most laboratories the tubes are set up with *serum dilutions as fol*lows 1 1, 1 2, 1 4, 1 8 1 16, 1 32, 1 64 1 128 1 256 Dilutions above 1 256 are frequently reported only as 256 which suffices for all practical purposes

*Quantitative serologic tests are particu*larly useful in following the course of treated early syphilis, in the consideration of biologic false positive reactions, and in the diagnosis of congenital syphilis in infants

There is no evidence indicating that the reagin titer is a measure of the extent or activity of the syphilitic process, although the average titer is much higher in secondary syphilis, paresis, gummas and cardiovascular syphilis than in late latent syphilis or in tabes

A word of caution is necessary in the interpretation of quantitative serologic tests Bearing in mind the dilutions of serum in the laboratory, the physician can readily see that the difference between a titer of 128 and 256 is no more than the difference between a titer of 1 and 2 units, namely a one tube variation Since day to day laboratory variation is universal, a one tube variation should be ignored and in the majority of laboratories, a confirmed three tube variation is necessary before concluding that a true change in reagin titer has occurred Thus a series of titers reported as "16, 32, 64 32, 32 indicates no change A series of titers reported as "16, 64, 128, 128 128 indicates the probability of serologic relapse In a treated patient a series of tests such as 1, doubtful, 1, negative, 1, negative, *doubtful* is indicative only of day to day laboratory variation in detecting the persistent small amount of reagin present

In treated syphilis, the value of serologic *negativity for determination of cure* depends not on a single test but on a series of tests carried out over a long period of time In general it is an excellent criterion in early syphilis and a poor one in late syphilis

The provocative Wassermann " formerly utilized as an aid to the diagnosis of syphilis is an artefact which rests on chance variations in the sensitivity of the laboratory tests and does not reflect an actual change in the serum reagin content In patients with primary syphilis with an already rising titer the continued temporary increase in titer after the initiation of treatment is purely

* See also Chapter 48

casualties infectious hepatitis, measles mumps scarlet fever, subacute bacterial endocarditis filariasis, leptospirosis, typhus brucellosis, tuberculosis and chronic endemic malaria There is no reliable evidence that the serologic tests are significantly affected by pregnancy or menstruation

In the absence of an indubitable history or clinical evidence of syphilis and in the presence of acute infection of other etiology or of recent inoculations it is well to avoid making a diagnosis of syphilis until the acute condition has entirely subsided and until sufficient time has elapsed to see if the tests may produce different results Under such circumstances repeated quantitative tests performed upon serial dilutions of serum are of inestimable value For a false positive reaction the trend in titer is usually downward whereas if syphilis is present the quantitative titer usually shows no definite change or may even increase In any case the pattern or trend of the quantitative tests is more important than the results of any individual test If at the end of six months no definite downward trend has been in evidence the chances are that one is dealing with syphilis because by this time false positive serologic tests due to other acute conditions have usually become entirely or almost entirely negative

In lepers and in patients with lupus erythematosus the diagnosis of syphilis cannot be made on serologic grounds alone In suspected infectious mononucleosis the blood smear and heterophile agglutination tests are of great importance At present it is impossible to prove or disprove whether endemic malaria or chronic tuberculosis produce false positive tests The former is almost completely an unknown quantity but the role of tuberculosis is thought to be negligible A false positive test with chancroid or lymphogranuloma venereum is unusual but for obvious reasons particularly difficult to detect The negative darkfields and absence of a high or rising titer with the quantitative test, coupled with the clinical appearance of the lesions are important suggestive points Expert consultation may be necessary to elucidate the problems raised by possible false positive reactions

Positive Reactions in Normal Individuals In actual practice, possible biologic false positive reactions occurring in otherwise apparently normal persons present a difficult problem The incidence has been estimated as 1 1000 to 1 4000 in clinically normal nonsyphilitic persons Characteristically these false reactions tend to be weak, the laboratory reports usually being doubtful or positive in low titer and the results obtained with two or more different tests may be conflicting This characteristic is however frequently of little assistance as many known syphilitics particularly those who have had the disease for years also have doubtful or weakly positive reactions It is usually impossible on serologic grounds alone to determine whether persons with persistent weakly positive or doubtful reactions are syphilitic or are normal false positive reactors

The Kahn verification test is not of value Such persons should be subjected to a careful history complete physical examination (including search for stigmata of congenital syphilis) repeated quantitative serologic tests by several technics examination of the cerebrospinal fluid and specialized laboratory studies including at least a blood smear heterophile agglutination test and search for lupus erythematosus cells Investigation of parents siblings and marital or sexual partners is of great importance Expert consultation is frequently essential, but if this is not available it is a good general rule to treat for syphilis in the absence of other obvious cause and when serologic tests by several technics in several laboratories remain positive for more than six months

Another method of grouping spinal fluid reports is to classify them as 'active' or 'inactive' on the basis of the cell count and total protein, particularly the former This is especially useful in post treatment observation because, under the influence of treatment, the cell count is usually the first to return to normal, the protein next, and finally, but much more slowly, the colloidal curve and Wassermann titer

False Positive Spinal Fluid Reactions

Biologic false positive spinal fluid Wassermann reactions are incomparably less frequent than are biologic false positive blood serologic tests Seven undoubted instances in nonsyphilitic persons have been observed at the Johns Hopkins Hospital, all confirmed by one or more repeat tests, and all subsequently becoming negative These patients were suffering from tuberculous, meningococcal, or benign lymphocytic meningitis Additional unconfirmed positive fluids were observed in 4 patients with subarachnoid hemorrhage, in 1 with poliomyelitis, and in 4 with bacterial meningitis The diagnosis of neurosyphilis based on a positive reaction to a Wassermann test of the spinal fluid alone is unjustified for patients suffering from meningitis and other acute intracranial disorders until repeated examinations, performed after these processes have subsided, demonstrate the continued presence of reagin In syphilitics during the course of meningeal infection of other etiology, transitory transfer of reagin from blood to spinal fluid may occur

Effects on Syphilis of Penicillin Used for Other Diseases

PENICILLIN administered for other diseases is not infrequently a source of confusion in the diagnosis and subsequent management of syphilis * This is particularly true in gonococcal infections In simultaneous infections, the gonorrhea may be treated with penicillin while the patient is in the incubation period of syphilis Under these circumstances the syphilitic infection may be aborted altogether the incubation period of the chancre may be prolonged or a completely symptomless infection may result The development of a positive serologic test for syphilis may also be delayed

All patients treated with penicillin for gonorrhea should be followed therefore, clinically and serologically once a *month* for at least four months Patients with gonorrhea who are known sexual contacts of cases of primary or secondary syphilis should be given streptomycin or sulfonamides until their syphilis status can be evaluated Penicillin should not be used for the treatment of gonorrhea when visible lesions suggestive of syphilis are *present* until after repeated dark field examinations and serologic tests have permitted an adequate *evaluation of the nature of the lesions.* A sharp febrile reaction within the first twenty four hours after the treatment of *gonorrhea with penicillin suggests* the presence of concurrent early syphilis

Patients given penicillin for the treatment of a variety of acute infections other than gonorrhea who are discovered after the initiation or completion of treatment to have a positive serologic test for syphilis frequently present a confusing problem This is particularly true because of the fre

* [illegible] and terramycin [illegible] produce confusion in the diagnosis and subsequent management of syphilis

coincidental and is not due to the treatment

A quantitative serologic test should always be obtained when a negative report is returned under circumstances where the physician strongly suspects syphilis This is because of the rare occurrence of the so called zone or prezone reaction with certain strongly positive sera In this situation for reasons not clearly elucidated such sera give a negative reaction undiluted but a positive reaction in high dilutions

SPINAL FLUID TESTS

An adequate laboratory examination of the cerebrospinal fluid must include cell count total protein determination colloidal reaction and quantitative Wassermann reaction The cell count should be determined within an hour after the fluid is drawn Ten or more white cells (lymphocytes) are definitely abnormal 6 to 9 cells borderline and less than 6 cells normal The upper limit of normal spinal fluid protein varies in different laboratories Usually less than 50 mg per 100 cc is considered within normal limits

The Pandy test may be used as a rough check on the total protein determination The colloidal reaction (gold mastic, benzoin reaction) is within normal limits when the curve does not contain a precipitation reading higher than 2 The type of zone precipitation observed (the so-called colloidal curve) is actually of no significance in the differentiation of clinical types of neurosyphilis Any type of curve may be produced by any kind of meningeal irritation The precipitation of colloidal suspensions is due to the presence in spinal fluid of increased amounts of globulin The particular zones of precipitation depend upon the albumin globulin ratio and not upon a specific diagnostic entity such as paresis The addition of gamma globulin to normal spinal fluid produces a paretic colloidal curve In the absence of a positive spinal fluid Wassermann, pleocytosis, protein elevation and an abnormal colloidal curve indicate meningeal irritation but not its etiology

Flocculation tests on spinal fluid are less satisfactory than the Wassermann test The proper interpretation of the spinal fluid Wassermann demands that the titer of the test be determined quantitatively Such titrations are of value in diagnosis and in post treatment evaluation The test on spinal fluid should be done with amounts of fluid ranging from 0 1 to 1 cc, and if it is positive with the smaller quantities, the titration should be carried downward No direct conclusions as to the type of neurosyphilis can be drawn from the spinal fluid Wassermann, but a strongly positive Wassermann is usual in paresis The so-called paretic formula in spinal fluids is usual in paresis but is not seen in all paretics and is seen in some patients with other types of neurosyphilis including asymptomatic neurosyphilis It corresponds with the Group III fluids discussed below and indicates a poor prognosis unless altered by treatment

Classification of Spinal Fluid Findings

It is customary to group spinal fluid reports according to degree of positivity into Groups I II and III *Group I* includes spinal fluids with negative Wassermann reactions but with pleocytosis and/or protein elevation and/or abnormal colloidal curves *Group III* includes those with maximal changes (the paretic formula) pleocytosis protein elevation, abnormal colloidal curve and a strongly positive Wassermann test with at least 0 2 cc. of spinal fluid (with such a report an anticomplementary Wassermann in a fluid freshly withdrawn may be considered to be the equivalent of a strongly positive report) *Group II* includes all spinal fluids of an intermediate type that is not falling into Groups I or III

ilitic osteitis or in the vicinity of a Charcot joint In the former situation antisyphilitic treatment can be expected to bring about union but under all other circumstances the results are usually disappointing and orthopedic procedures are necessary

Morale of the Patient The knowledge of infection with syphilis for many patients causes a sense of shame and disgrace which may often result in severe psychiatric complications The patient must be made to realize that syphilis is a disease, not a sin that health, not morals is the primary consideration and that with proper treatment any of the normal life relationships are possible including marriage and childbearing The facts of infectiousness must be carefully explained

Economic Status The economic status of the patient must be frankly faced at the outset It is the duty of the physician to see that his patient is properly treated, if not by himself, then by a colleague, a health department, a hospital clinic or a federal rapid treatment center Data concerning public treatment facilities available in a particular community can be obtained from the local, county or state health department Patients with infectious syphilis who lapse from treatment or observation should be followed by the physician or turned over to the health department for disposition

Technical Aspects of Treatment

ARSENICALS

Intravenous Injection

In the present-day treatment of syphilis, the intravenous injection of arsenicals is rarely indicated

Intramuscular Injection

The optimum site for injection is the upper outer quadrant of the buttock An 18 or 19 gauge needle two to two and a half inches long is recommended The syringe is filled with the substance to be injected before the needle is attached and the needle is inserted separately because if a blood vessel is accidentally entered blood will flow from its hub If blood does not appear the syringe is attached and aspirated If blood is not obtained on aspiration the injection may be made This double precaution against accidental intravenous injection is absolutely essential as frequently a vein is entered accidentally Should an oil suspension be inadvertently administered intravenously serious and even fatal pulmonary oil embolism may result

LUMBAR PUNCTURE

This is an integral part of the management of all patients with syphilis The technic can be acquired only by practice under supervision The necessity for lumbar puncture will be understood by most patients after explanation of the frequency of nervous system involvement in syphilis and of the advantages of early recognition of this involvement Examination of the optic discs should precede lumbar puncture since the procedure is in general contraindicated in the presence of choked disc except under the supervision of a neurosurgeon In the presence of acute infections lumbar puncture is also best deferred because of the possibility of transfer of organisms from blood to the cerebrospinal canal due to alteration in the blood-spinal fluid barrier by withdrawal of spinal fluid Other relative contraindications to lumbar puncture include recent subarachnoid or extradural hemorrhage advanced age advanced pregnancy or illness from other

quency of biologic false positive serologic tests with acute febrile illnesses When penicillin has been given and the serologic test for syphilis subsequently becomes negative it may be almost impossible to decide whether this is the spontaneous subsidence of a false positive serologic test for syphilis or the response of an early syphilitic infection to treatment

Such patients should be studied as outlined under the section on biologic false positive serologic tests and should be subjected to contact investigation, lumbar puncture, and follow up as for a known syphilitic infection even though the diagnosis may not be indubitable Further treatment, if it is decided that syphilis is present, depends upon a precise evaluation of the clinical type, examination of the spinal fluid and the amount of penicillin already given In general if such a patient has not received the amount of penicillin suggested in the various sections which follow retreatment is in order

General Considerations Affecting Treatment

Physical Examination A complete physical examination must be performed before treatment is started This should be preceded by an adequate history to include details directly concerning the syphilitic infection family and marital history and a complete review of the systems Syphilis may involve almost any structure in the body The type of treatment intensity of follow up and prognosis will vary depending on the duration of infection and the type and degree of involvement by the disease Moreover it is important to detect the presence of complicating diseases which may alter the prognosis or affect ability to tolerate treatment The latter is particularly pertinent if the use of arsenicals or fever therapy is contemplated We know of no condition which contraindicates penicillin therapy other than a history of hypersensitivity to the drug itself Last but not least is the value of the initial physical examination in establishing a base line for measuring possible progression of the disease in after years

Age and Physical Condition The age and general physical condition are of importance not only in determining the type of treatment but also frequently in determining whether to allow the patient to go entirely untreated Early syphilis must of course always be treated because of the infectious nature of the disease but latent syphilis in patients over the age of 60 years may generally be allowed to go untreated If late active lesions are present at any age some treatment probably will be essential for symptomatic relief

Surgery The advent of penicillin has simplified the problem of surgery in a syphilitic since the drug can be given both pre and postoperatively if indicated after proper examination and evaluation of the situation in the individual patient There is no reason for deferring operation until the blood tests are negative which may be impossible of attainment Wound healing occurs as rapidly in those infected with syphilis as in those free of this disease and infectious persons are rendered noninfectious within a few hours after penicillin treatment is begun Operations directly upon unrecognized and untreated gummas, however usually end disastrously Syphilis plays no real role in ununited fractures except where the fracture occurs in an area of actual syph

most adequate facilities are available in the *hospital with which* he is associated

All forms of fever therapy are potentially dangerous procedures requiring close observation, and none should be attempted in the home Physicians lacking practical experience in this form of treatment should secure it under supervision before personally assuming complete responsibility for any patient

Fever Therapy Since the advent of penicillin, the indications for the use of fever therapy are few When this treatment is employed, the patient's general physical condition should be carefully determined by preliminary, complete physical examination and laboratory studies which should include as a minimum a complete blood count, urinalysis, and a roentgenogram of the chest Routine electrocardiography is advisable in all candidates over 40 years of age Renal function tests and liver function tests should be obtained when there is the slightest suspicion of impaired function of either of these organs

Contraindications to Fever Therapy Among the absolute contraindications to fever therapy are active pulmonary tuberculosis advanced age (usually over 60 years), extreme malnutrition, aortic aneurysm unless it is calcified, malignant hypertension, hyperthyroidism until controlled, severe anemia until corrected, active rheumatic fever, chronic nephritis with impairment of renal function Laennec s cirrhosis congestive heart failure or severe myocardial insufficiency and any other condition, such as carcinomatosis, the intrinsic prognosis of which is so poor that treatment of the neurosyphilis is of minor importance Relative contraindications are many and what to do under such circumstances is a matter of individual clinical judgment As examples of relative contraindications one might cite inactive pulmonary tuberculosis, mild angina pectoris unregulated diabetes mellitus, valvular heart disease of rheumatic or syphilitic origin, and extreme obesity There are many others too numerous to mention

Penicillin

Procaine Penicillin

Penicillin in aqueous solution is rapidly absorbed and excreted, largely in the urine Until the advent of procaine penicillin, the most satisfactory method of delaying the absorption of penicillin was to administer it suspended in peanut oil and 4 8 per cent beeswax Procaine penicillin has now completely supplanted penicillin in oil and wax It is the water insoluble procaine salt of benzyl penicillin containing one molecule of penicillin G combined with one molecule of procaine base (0 12 Gm of procaine per 300 000 units) This amount of procaine is of negligible toxicity since the lethal dose is of the order of 4 8 Gm *Its safety is further enhanced* by the slow release of the procaine from the insoluble procaine penicillin In those few persons who are unusually sensitive to the stimulant action of procaine on the central nervous system, any of the common barbiturates will serve as an effective antidote

Rare idiosyncratic death may occur following the administration of as little as 10 mg of procaine All patients to whom procaine penicillin is to be administered therefore should be queried regarding prior reaction to procaine To our knowledge such idiosyncratic reactions have not yet been reported in actual practice At this time, the most consistently prolonged

cause so serious as to make the information provided unimportant

Complications

Aside from headache, the complications of lumbar puncture are rare Sudden death has occurred due to herniation of the brain stem into the foramen magnum in instances of unrecognized or ignored subtentorial brain tumor Meningitis has occurred from faulty, unsterile technic Subarachnoid hemorrhage with extraocular muscle palsies has occurred several hours after the puncture Recovery from this latter complication is usually prompt and complete Ruptured intervertebral disc has also been reported but is very rare

Headache

Lumbar puncture headache occurs in many patients who are subjected to the procedure on an ambulatory basis It may be minimized in hospitalized patients by performing the puncture with the patient in a horizontal position this position being maintained for twenty four hours A small needle (20–23 gauge) reduces the incidence of headache This type of headache is unique in that it disappears as soon as the patient lies down and reappears as soon as he assumes the erect position It is not infrequently associated with dizziness nausea and vomiting

In some patients there is extreme nuchal aching and stiffness The onset is usually several hours after performance of the puncture It is not relieved by drugs and is of such severity that bed rest in the horizontal position is essential Whether to advise such bed rest at home for all ambulatory patients is questionable as there is no convincing data that thereby the incidence of headache may be reduced Patients frequently become greatly alarmed by the headache and require a careful explanation in advance and a warning that while the average duration is about forty eight hours not infrequently recurrences are experienced for a week or two whenever the erect position is assumed

A cell count on the spinal fluid must be done without delay to avoid error due to dissolution of cells A simple method is to place one drop of concentrated acetic acid (to 50 cc of which several drops of methyl violet or gentian violet have previously been added) directly into the last tube containing 0 5 to 1 cc of spinal fluid This causes laking of any red blood cells which may be present and at the same time stains the nuclei of the white blood cells The fluid is then placed in a counting chamber with a white cell pipette and the cells in all the squares are counted under low power High power can be utilized for verification of questionable cells The total count multiplied by 10/9 is the number of cells per cubic millimeter of spinal fluid

FEVER THERAPY

The commonly utilized forms of fever therapy include malaria inoculata fever induced by the intravenous injection of typhoid vaccine and artificial (cabinet) fever therapy No attempt will be made here to discuss the relative merits of these three forms of therapeutic fever Some workers in the field believe that the results attained are related to the amount rather than to the type, of fever therapy given Since it is more difficult to attain satisfactory sustained temperature levels with typhoid vaccine its utilization is recommended only if malaria and artificial fever therapy are not available, or as a substitute for malaria in patients refractory to inoculation Although [illegible]

son of these two therapeutic methods in paresis failed to demonstrate this supposed superiority The physician should utilize the form of fever therapy for which the

havior with bacteria that penicillin acts only against rapidly multiplying treponemes in the active stage of growth It is probable that the direct bactericidal or treponemicidal action of penicillin is largely responsible for its therapeutic activity Experimental evidence indicates that the outcome of therapy is not adversely affected by failure to maintain a constant concentration of penicillin in the blood The important therapeutic factor apparently is exposure of the spirochetes to adequate tissue concentrations of penicillin for an adequate but not necessarily continuous period of time Exposure to relatively low tissue concentrations over a long period is more effective than high concentrations maintained for a short period of time Prolongation of the treatment period is a highly promising approach to greater therapeutic efficacy

Toxicity

Penicillin is a remarkably nontoxic drug but at least one instance of death due to the drug has been reported It involved an acute exfoliative dermatitis together with jaundice Intramuscular injections have rarely led to cellulitis or abscess of the buttock and local pain is almost absent when procaine penicillin is used Secondary fever developing five or more days after beginning therapy sometimes occurs but with currently available purified products this is rare

Cutaneous reactions probably allergic, are observed in about 1 per cent of patients Most of these are urticarial Penicillin in oil and wax or procaine penicillin may cause an isolated giant hive which may persist for days at the injection site Other rashes include generalized erythematous macular maculopapular vesicular, and true exfoliative dermatitis In some patients with pre-existing epidermophytosis of the feet or groin penicillin causes the fungus ... to become acute (dermatophytid) None of these cutaneous reactions are serious as a rule and all disappear promptly when the drug is stopped

A rather alarming and often prolonged delayed reaction may rarely develop similar to serum sickness with fever, urticaria painful serous hydrarthrosis and sometimes exfoliation of the palms Unusual reactions which have been reported include an Arthus type of response anaphylactic shock agranulocytosis, anaphylactic purpura with toxic nephritis and severe almost fatal asthma occurring for the first time after penicillin

In all of the allergic types of reactions particularly in urticaria and the serum sickness syndrome the antihistamine drugs are of considerable value Epinephrine in oil is also of some value in the urticaria and serum sickness syndrome In the rar... severe reactions penicillin therapy shoul... be permanently discontinued but in th... usual urticarial or other mild cutaneo... reactions it can often be resumed es... cially if one of the antihistamines is gi... concurrently

Jarisch Herxheimer Reaction The ... (therap... isch Herxheimer reaction (therap... shock) may occur after the use of ... rapidly acting treponemicidal drugs a... perhaps more frequent with pen... than with the arsenicals With slow... ing agents such as the insoluble b... salts it is practically never observed... reaction is characterized by a gene... a focal component assumed to be ... the rapid destruction of large nu... *T pallidum* With early syphilis ... injection is followed in a few ... elevation of temperature to 100... This usually disappears withi... hours At the same time there ma... sification of primary or second... of brief duration The pain of b... is usually intensified during the ... four hours after injection Fe... heimer reactions were observe...

blood levels are attained by a product in which the particle size of the procaine penicillin suspended in oil is less than 5μ to which is added 2 per cent aluminum monostearate as a dispersing agent The aluminum monostearate aids in maintaining the dispersion of the small particles of crystalline procaine penicillin G and also increases the ability of the preparation to repel water thus delaying the absorption and prolonging the effect of penicillin In most instances a single injection of 600 000 units (2 cc.) provides measurable blood concentrations for forty eight to ninety six hours Procaine penicillin is also available for aqueous suspension and in this form will give higher initial levels but it maintains a measurable blood level for only twenty four hours Procaine penicillin is the drug of choice for the ambulatory treatment of all stages of syphilis

Systemic Dispersion of Penicillin

Although penicillin given intramuscularly or intravenously apparently does not diffuse well into the cerebrospinal fluid abundant clinical evidence indicates that excellent results may be accomplished in neurosyphilis without the use of intrathecal injections Further there is doubt as to whether the presence of a given drug in the cerebrospinal fluid has any bearing on its therapeutic efficacy the drug is carried to the diseased tissues of the central nervous system by the blood system rather than by the cerebrospinal fluid There is some evidence that penicillin is present in the spinal fluid but is in a bound form However penicillin diffuses well into the placental and fetal circulation Penicillin administered to the mother appears in the amniotic fluid and fetal tissues as early as the tenth week of gestation

Penicillin Resistance

The long-observed phenomenon of the development of arsenic and bismuth resistant strains of *T pallidum* has not th been seen with penicillin Clinical early syphilis, no clear cut examples c penicillin resistance (persistent p dark field and failure of lesions to have been observed Relapses which in about 5 per cent of patients t have always healed with retreatmen indubitable example of true penicil sistance however, has been observ a gummatous lesion which resp promptly to metal chemotherapy afte ing failed to occur with adequate of penicillin It can nevertheless be with assurance that penicillin resista extremely rare

Prophylaxis with Penicillin

It has been demonstrated in rabbit with a fixed inoculum of treponem curative dose of penicillin given duri incubation period of the infection is smaller (one thirty second of the dose the curative dose similarly administe the established infection This sugg new approach to the prophylaxis of lis because syphilitic infection in r usually susceptible to abortion with tively small but promptly admin doses of penicillin This suggestio been applied with apparently fav results to the prophylactic (or tive) treatment of persons exposed by sexual contact with a known inf syphilitic One 600 000 unit injecti procaine penicillin apparently prot high proportion of such exposed p On the other hand experimental indicate that once infection is estab in the rabbit late syphilis of six m duration (corresponding roughly t latent syphilis in man) is as easily cu early syphilis of six weeks duration

Action of Penicillin

This is rather good evidence agai suggestion based on analogy to

and if the patient becomes serologically negative and remains clinically negative, it should be repeated at the end of two years If then negative, and subsequent progress is uneventfully favorable, the spinal fluid need not be again retested In cases of clinical or serologic relapse or seroresistance at one year, the spinal fluid should always be re examined During the second and third year of follow up recheck inspections and serologic tests may be performed at intervals of three months In later years serologic tests every six months and an annually repeated physical examination are desirable

Re-treatment

The indications for re treatment are reinfection, clinical relapse serologic relapse, seroresistance, or an abnormal cerebrospinal fluid By the term clinical relapse is meant the reappearance of any clinical evidence of syphilis Included in this category are reinfection infectious mucocutaneous relapse (because they frequently cannot be differentiated), neurorelapse ocular relapse osseous relapse, or, for a woman the birth of a congenitally syphilitic infant Serologic relapse is the return of the serologic test for syphilis to positive in a patient who had previously become seronegative, or, in a patient who had had a falling quantitative titer a subsequent sustained significant rise in titer Serologic relapse frequently portends clinical relapse

Seroresistance Seroresistance has been variously defined Re treatment is in order after six months post treatment observation if there is not discernible a significant downward trend in serologic titer as compared with the pre treatment level In addition patients who have not become seronegative within the first year after treatment and whose titer by a quantitative test at the end of that time is 8 dilution units or higher, should be re treated The major ...nts who have a persistent low titer serologic test for syphilis (less than 8 units) at the end of the first year, become seronegative during the second or third post treatment year without re treatment

A positive cerebrospinal fluid is, in general, an indication for re treatment A completely inactive fluid (see section on interpretation of spinal fluid reports) at six months, however, may be "on the way down from a more strongly positive pre treatment fluid Under these circumstances it is permissible to withhold re treatment and repeat the examination six months later If the spinal fluid is still positive, re treatment must then be given

In patients re treated with penicillin alone following failure from original treatment and regardless of the total re treatment dose, failure rates are higher than i patients treated for the first time At lea a partial explanation for this is found seroresistance This in turn may be plained by longer duration of infection the re treatment group Re-treatment m than one year after infection canno expected to affect favorably the sero test for syphilis uniformly By this the biology of the disease is changin seroresistance is common even in p treated for the first time at this stage infection

Re treatment should be by pe alone in double the dose and dou duration of the original treatment

A second re treatment course sh be given for seroresistance alor chance of effecting seronegativity remote For a second serologic relapse, the patient should be with the same amount of penic the first relapse

Seroreversal

The rate at which serore after penicillin treatment of depends to some extent on th infection before treatment a

cent of 939 patients with early syphilis treated with crystalline penicillin G. Over a wide dosage range (10 to 120 000 units/Kg body weight) the incidence and severity of febrile reactions were remarkably constant. The Herxheimer reaction in the various types of late syphilis is discussed elsewhere.

EARLY SYPHILIS

Although some uncertainty still exists concerning the optimum time-dose relationship of penicillin in the treatment of early syphilis and also concerning its efficiency relative to metal chemotherapy, the consensus is that penicillin given alone is the optimum initial treatment for primary and secondary syphilis. Its relatively negligible toxicity, ease of administration, and the fact that almost all patients complete treatment, rather than its greater therapeutic efficacy, are the chief reasons for its almost universal adoption. It has further been demonstrated that crystalline penicillin G is better than amorphous penicillin, that penicillin in absorption delaying media is as good as aqueous penicillin, and that the results are better in primary than in secondary syphilis. It is also quite clear that the results of penicillin therapy are somewhat better than available data indicate because of the inclusion of an undetermined number of reinfections as treatment failures.

Dosage Schedules

Available clinical data fail as yet to detect any significant difference in efficacy whether aqueous penicillin is given every two, three or six hours, whether in total dosage of 2.4, 4.8 or 9.6 millions of units, whether given over a period of four, seven and a half or fifteen days, and whether given alone or with concurrent metal chemotherapy. With the absorption delaying penicillins, because of their more recent introduction, even less is known about the optimum time-dose relationship. The physician will recognize that any specific time-dose recommendations for the treatment of early syphilis are purely arbitrary. It is felt that in a disease with the potentialities of syphilis the conservative course is to utilize the larger dosage of the drug, even though the advantage of larger dosage has not been demonstrated statistically.

Hospitalization is not necessary for the treatment of early syphilis, but if the patient is in the hospital, it is recommended that aqueous crystalline penicillin G be given in a total dose of six million units over a ten-day period. This may be given as 150 000 units every six hours or 75 000 units every three hours. For ambulatory treatment, it is recommended that 600 000 units (2 cc) of procaine penicillin with aluminum monostearate be given daily or every second day until a total of six million units has been given. An alternate schedule recently authoritatively suggested consists of 2 400 000 units initially, followed by 4 injections at four-day intervals of 600 000 units each.

Early latent syphilis of less than two years duration should be treated and followed in the same manner as are primary and secondary syphilis. Early syphilis that is treatment-resistant after previous metal chemotherapy may be successfully treated with penicillin administered on the same schedule as for previously untreated early syphilis.

Follow-up

After treatment is completed, the patient is asked to return at monthly intervals, at which time he is stripped and examined for infectious relapse and blood is withdrawn for a quantitative serologic test for syphilis. Any suspicious lesions are subjected to dark-field examination. The initial spinal fluid examination is performed six months after the completion of treatment. If the results are entirely negative,

nign Late Syphilis

Benign late syphilis is an allergic type with inflammatory (often gummatous) lesions usually involving the bones or the skin and mucous membranes or rarely, breast tendon muscle or joint sometimes with the production of juxtarticular nodules In 20–25 per cent of these patients there is concomitant cardiovascular vis ceral or neurosyphilis The routine use of lumbar puncture is essential in benign late syphilis The Herxheimer reaction is not important in late mucocutaneous syphilis In patients with osseous lesions there is often an intense exacerbation of bone pain within twenty four hours after the initia tion of treatment A febrile Herxheimer may occur in latent or any type of benign late syphilis

In mucocutaneous lesions healing is usually rapid even the largest lesion cica trizing in six to eight weeks In periostitis symptomatic relief is prompt whereas for osteitis or osteomyelitis it may require weeks If sequestration occurs surgical inter vention for the removal of sequestra may be necessary in addition to antisyphilitic treatment before healing is complete Skin grafting of large secondarily infected ulcerating skin lesions which overlie diseased bone is necessary on rare occasions Failure of benign late syphilis to heal under treatment is usually due to secondary in fection bone sequestration or as in gum matous ulcers of the legs in patients with peripheral arteriosclerosis or varicose veins to a poor vascular supply or stasis In the latter situation leg ulcers in elderly syphi litics with varicose veins are usually of vari cose (static) rather than of gummatous origin especially if they occur in the vari cose area over the lower third of the tibia and if they are surrounded by varicose eczema Such ulcers cannot be expected to heal under antisyphilitic treatment alone
osseous syphilis improvement as
tgenographic examination

seems to lag far behind symptomatic im provement Indeed early post treatment films may show actual progression In most instances the lesion is proliferative with new bone formation in these the x ray picture shows little change even over a period of years The less common destruc tive lesions show on roentgenographic ex amination a gradual deposition of new and healthy looking bone in the diseased area

Antisyphilitic treatment of any type does not abolish the allergic tendency Regard less of type or amount of treatment subse quent relapse usually also gummatous in nature may occur

Treatment Although definitive state
ments cannot yet be made in regard to the
ultimate clinical outcome and dosage
schedules of penicillin in benign late gum
matous syphilis the immediate results
penicillin therapy are as favorable as t
more prolonged and dangerous m
chemotherapy Failure of lesions to
with penicillin is usually due to cause
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cillin resistance The latter does oc
benign late syphilis but is much l
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Penicillin is recommended as
ment of choice for benign late s
dosage of six million units by
identical with those used for e
and latent syphilis If after su
has elapsed healing has not
treatment should be given wi
dose of penicillin and for do
period In such instances
factors such as secondary
sequestration poor vascu
stasis should be especially
for and eliminated if p

Surgical operations on
untreated gummatous
studiously avoided Al
cedures end disastro
spread of the gumm

sitivity of the serologic test for syphilis used On the average a negative serologic test for syphilis is attained between the fourth and seventh month after treatment The critical period for the development of clinical or serologic relapse is between the fourth and ninth month after treatment, though relapses, or reinfections, have been observed as early as one month and as late as three years One of the objectives of therapy in early syphilis is seronegativity Although the exact significance of seroresistance for the individual patient in terms of ultimate clinical outcome is not clear, it is known and has been well documented by long term studies with arsenical treated patients that most of the clinical failures *ultimately come from this group*

LATENT, BENIGN LATE, AND VISCERAL SYPHILIS

Symptoms or physical signs of the disease do not occur in latent syphilis and the spinal fluid is normal Early latent syphilis should be treated and followed after treatment similarly to primary and secondary syphilis Late latent syphilis (duration more than two years) is most frequently encountered by the practitioner

Latent Syphilis

Treatment of late latent syphilis is intended to prevent the development of late clinical manifestations of syphilis In syphilis of more than four years duration seroresistance is the rule Moreover, relationship has not been demonstrated between serologic response and clinical outcome in either late latent syphilis or in late *syphilis with clinical manifestations* Examination of the cerebrospinal fluid should precede treatment in patients with syphilis of more than two years duration If the fluid does not show abnormal findings reexamination is not necessary because in almost all patients neuraxis invasion if it occurs, is during the first two years of infection

After completion of treatment for late latent syphilis, the patient should be observed at yearly intervals for evidences of clinical progression It is not necessary to make monthly blood tests, although a quantitative serologic test for syphilis should be performed every six to twelve months In some treated seroresistant patients, the serologic test for syphilis later becomes spontaneously negative without further treatment Re treatment, in the absence of pregnancy, should not be given for a persistently positive serologic test for syphilis with stabilized titer, but only for proved or suspected clinical progression *It is probable that patients with indubitable* verified serorelapse (see section on quantitative serologic tests for syphilis) should also be re-treated

Treatment Although documentation is not available concerning the efficacy of penicillin in late latent syphilis, this drug has been used for the following reasons (1) the prognosis in late latent syphilis is good in any case (2) penicillin cures latent syphilis in rabbits (3) since penicillin cures early syphilis and arrests late syphilis, it should be of preventive value in latent syphilis (4) penicillin therapy is relatively free from reactions and is brief (5) the *theoretical objection that penicillin* acts only on dividing but not on resting organisms is based on work with bacteria not treponemes and moreover a resting state of *T pallidum* is not yet a completely *established fact even though clinical latency* may exist

Late latent syphilis may be treated with the same schedules of penicillin therapy used in the treatment of early syphilis In seroresistant patients adequately treated with metal chemotherapy previously, the subsequent use of penicillin does not appear to produce additional clinical or serologic results

he first year and semi yearly thereafter, as for benign late syphilis When, as is more usual the diagnosis is in doubt and treatment has been more in the nature of a therapeutic test follow up must be more intensive and individualized with a view to attempting to determine the effectiveness of treatment on symptoms physical signs and radiologic findings Re treatment for late visceral syphilis should be given only when there is clinical relapse or verified serologic relapse and should consist of repetition of the original course of treatment

CARDIOVASCULAR SYPHILIS

Cardiovascular involvement the most frequent basic cause of death from acquired syphilis can be almost completely prevented by the adequate treatment of early syphilis Even if treatment is first given in the latent stage of the disease it is rarely followed by clinically manifest cardiovascular involvement

Aortitis

Uncomplicated syphilitic aortitis is usually not clinically recognizable and treatment is given as for latent syphilis That this suffices is borne out by the excellent prognosis of clinically latent syphilis which yields a large proportion of uncomplicated syphilitic aortitis at autopsy usually unrelated to the cause of death An occasional patient with clinically latent syphilis (uncomplicated syphilitic aortitis) will however develop aortic regurgitation or aneurysm even after adequate treatment Under such circumstances it is not clear whether one is dealing with simple progression or with the so called therapeutic paradox resulting from scar tissue due to healing Such untoward results are however, unusual The ideal method of treatment of cardiovascular syphilis therefore lies in proper therapy before the development of clinical evidence of cardiovascular involvement Reasonable assurance can then be given that clinical cardiovascular syphilis will not develop

Treatment

The treatment of clinical cardiovascular syphilis (aortic regurgitation saccular aneurysm and aortitis with coronary osteal stenosis) is a controversial subject It is probable that for years therapy will be based on clinical impressions rather than upon biostatistical proof Nevertheless some consider that antisyphilitic treatment has been of definite value in both relief of symptoms and prolongation of life in aortic insufficiency and aneurysm

In patients who have developed aortic insufficiency or aneurysm a rigidly outlined scheme of treatment cannot be substituted for a sound knowledge of internal medi cine The proper use of digitalis mercuria and other diuretics and the limitation o activity and salt intake is often life saving If as is desirable, the patient is in t hospital ten to twenty million units aqueous penicillin may then be given o a period of fifteen to thirty days This be given as 150 000 units every six hou 75 000 units every three hours For am tory treatment the use of procaine cillin with aluminum monostearate 6 units (2 cc) daily or every second da a total of ten to twenty million un been given is recommended

Admittedly the therapeutic effi such treatment is not known It mended on a basis of lack of brevity ease of administration an that the therapeutic efficacy of me therapy also is unknown The fe recognizable cases of uncomplic litic aortitis and of aortitis wi osteal stenosis may be treated ing to the above outline

Aneurysm Saccular aneur ripheral arteries in the extre

* See also Chapter 10

Plastic repair of healed gummatous lesions of the nasopharynx, no matter how well previously treated should be preceded and followed by penicillin therapy

Follow up After completion of treatment for benign late syphilis, the patient should be observed and a quantitative serologic test for syphilis taken at intervals of three months for the first year and semi yearly thereafter indefinitely Re treatment should not be given for a persistently positive serologic test for syphilis, but only for proved or suspected clinical relapse, or for verified serorelapse Gradual spontaneous disappearance of reagin from the blood during the years of post treatment observation is not unusual

Re treatment for benign late clinical relapse or verified serologic relapse should consist of repetition of the original course of treatment

Visceral Syphilis

Visceral syphilis exclusive of cardiovascular and neurosyphilis, is usually gummatous in nature and occurs relatively late in the course of the disease In early syphilis, one may encounter as unusual manifestations in addition to periostitis and osteitis early syphilitic hepatitis and syphilitic nephrosis The diagnosis in such instances is not difficult because of the concomitance of mucocutaneous lesions of secondary syphilis It can best be confirmed by the therapeutic test Penicillin is especially suitable for the treatment of early syphilis complicated by hepatitis or nephrosis since it is nontoxic and does not impose an additional chemical aggravation to the already damaged hepatic or renal parenchyma The usual dosage and schedules for early syphilis may be used

The proper management of late visceral syphilis depends less on the particular method of treatment utilized than on accurate differential diagnosis A discussion of diagnosis is beyond the scope of this monograph but the physician should bear the following facts in mind (1) syphilis, as it affects the viscera, is relatively rare and benign as compared with other disease processes with which it is often confused (such as carcinoma, tuberculosis, or portal cirrhosis), (2) the longer the process has existed especially in the absence of sig

benignity (often with few or no symptoms) is exceedingly difficult and is generally one of exclusion (4) the therapeutic test as an aid to diagnosis is of limited value (this is particularly true when the differential diagnosis is between syphilis and carcinoma in an operable site, delay in awaiting the often ill defined and slow results of the therapeutic test under such circumstances may prove disastrous by allowing an operable to become an inoperable carcinoma) (5) direct methods of diagnosis such as biopsy or exploratory operation are usually preferable to the therapeutic test where feasible This is particularly true in lesions of the stomach

Treatment Penicillin has been utilized successfully in the treatment of gummatous syphilis of the larynx lung and liver *A priori, there is not any reason why it should* not prove equally successful in the treatment of other forms of late visceral (tracheal thyroidal bronchial mediastinal esophageal gastric) syphilis Because of its freedom from toxic effects it is recommended as the treatment of choice for all forms of visceral syphilis The dosage schedule suggested is identical with that recommended for early latent and benign late syphilis

Follow up After completion of treat

diagnosis is certain it is sufficient to follow patients at intervals of three months for

neuroretinitis or optic neuritis, or extensive inflammatory lesions of choroid or retina As with all scar tissue, they are uninfluenced by antisyphilitic treatment but are also nonprogressive The treatment of syphilitic primary optic atrophy is discussed subsequently in the section on the treatment of neurosyphilis

Uveitis

The commonest ocular manifestation of early syphilis, anterior uveitis (iritis cyclitis and iridocyclitis) responds well to treatment as previously outlined for early syphilis In early syphilis the cornea is rarely involved *Like optic neuritis, anterior uveitis may occur in* association with secondary syphilis or as a monorecidive, and is often especially when it occurs as a relapse accompanied by neurosyphilis Aggravation of the ocular inflammation practically always *occurs within the first day* of treatment (Herxheimer effect) but does not leave permanent untoward sequelae

The association of uveitis (anterior uveitis or choroiditis) or kerato uveitis with late *syphilis offers a difficult problem* Some physicians are becoming increasingly convinced that the failure of many of these cases to respond to any form of antisyphilitic treatment is because syphilis may be merely a coexistent rather than an etiologic factor Nevertheless where uveitis is associated with late or otherwise latent syphilis the therapeutic test should be instituted without delay to minimize permanent ocular damage The principles of treatment are the same as those for late syphilis in general and the Herxheimer reaction is in*frequent and not of importance* Penicillin is the drug of choice Both metal chemotherapy and penicillin may exert a non specific salutary effect on uveitis of other etiology Therefore unless dramatic results are obtained the therapeutic test must be interpreted cautiously The discovery of a positive serologic test for syphilis in a pa*tient with uveitis should not* be taken signal to abandon all attempts to inv gate other possible causes of the oc lesion Local ophthalmologic treatmen uveitis should be in the hands of ophthalmologist *Disseminated choroic* in late congenital syphilis is a residuum pre existing inflammatory lesions and not respond to antisyphilitic treatmen

Interstitial Keratitis

Interstitial keratitis is the commor lesion of late congenital syphilis and *may occur, rarely in acquired syph* About one half of all patients with congenital syphilis seek aid because of Usually there is accompanying uveal t*involvement often severe Interstitial ke*titis is at present one of the outstand enigmas of syphilotherapy because of great variability in response to all types treatment Some cases respond rapidly minimal treatment others are *seemin* refractory to all treatment Still other ca occur for the first time or recur in the m of, or after presumably adequate treatme *With any form of treatment Herxhein* reactions are for practical purposes abse

The hope that penicillin might be great value in this condition has not be realized Neither penicillin nor any otl form of treatment eliminates industr blindness (final visual acuity 6/60 or le in a considerable proportion (5 to 10 p *cent) of patients treated Although it is t* consensus of experts in the field that fev therapy is the treatment of choice, the sar criticism holds true for this form of thera as for penicillin—lack of statistically val demonstration of therapeutic efficacy w respect to the prevention of blindness

Some patients will respond to treatmen therefore all should be treated Penicilli ten to twenty million units over twelve twenty days may be given as the init form of treatment either in the hospital on an ambulatory basis It is recommende

be managed by surgery supplemented with antisyphilitic treatment Wiring and electrolysis of thoracic and abdominal aneurysms is practiced in some large centers It requires special equipment and interest on the part of the surgeon An occasional otherwise hopeless case is greatly benefited Preliminary angiocardiography is almost essential both in determining the exact location of the aneurysm and the presence or absence of clot Numerous other surgical procedures have been attempted, discussion of which is beyond the scope of this chapter

Herxheimer Reaction The question of the Herxheimer reaction in cardiovascular syphilis has been re-opened by the advent of penicillin therapy The natural course of the disease includes sudden death and sudden congestive failure If one of these occurs during or soon after treatment, there is no way of knowing whether there is a true etiologic or merely a coincidental temporal relationship to treatment Even postmortem examination usually does not supply the answer At the Johns Hopkins Hospital, penicillin has been administered as the initial form of treatment to more than 100 carefully followed patients with aortic regurgitation or aneurysm (and doubtless to hundreds more with unrecognized aortitis) Nothing which we could definitely attribute to therapeutic shock has been noted A few Herxheimer reactions have been reported in the literature, but it is difficult to be certain of their authenticity

Follow-up

After specific therapy is completed, the patient with cardiovascular syphilis should be kept under close observation, the frequency of which is determined by the presence or absence of symptoms of heart failure, angina or aneurysmal compression Since progression is the natural course of the cardiovascular process, re treatment should be given only as indicated for other manifestations of late syphilis The titer of the serologic test for syphilis is not of importance in late cardiovascular syphilis and seroresistance or serorelapse do not constitute criteria for re treatment.

OCULAR SYPHILIS*

In the management of ocular or suspected ocular syphilis, ophthalmologic consultation is necessary for accuracy of diagnosis and evaluation of the effect of treatment Chancre of the conjunctiva, gummatous episcleritis, and gumma of the orbit do not present special problems, their treatment being that of the corresponding stage, early or late, of the systemic infection In all, response to treatment is excellent, and the Herxheimer reaction is of little or no importance

Optic Neuritis

Optic neuritis due to syphilis does not differ in appearance from optic neuritis of other etiology and may even be difficult to differentiate ophthalmoscopically from papilledema due to increased intracranial pressure It may occur in association with secondary syphilis, as a monorecidive in previously untreated or inadequately treated early syphilis, and occasionally as a manifestation of late syphilis It is sometimes accompanied, especially when it occurs as a relapse, by a positive cerebrospinal fluid and sometimes by other clinical evidence of neurosyphilis Response to penicillin is excellent, and the Hexheimer reaction, if it occurs at all is unusual Treatment with penicillin as outlined in other sections of this monograph for the appropriate stage of syphilitic infection, early or late, is recommended as the therapy of choice

Optic Atrophy

Secondary optic atrophies are the result of scar tissue occurring as the end result of

* See also Chapter 37

parenchyma are all involved and the clinical diagnosis depends on whether the predominant process is meningovascular or parenchymatous inflammatory or degenerative

Those clinical syndromes which are predominantly meningeal and inflammatory (all instances of early asymptomatic neurosyphilis some of late asymptomatic neurosyphilis syphilitic meningitis and a large group with late unclassified neurosyphilis) respond well to treatment To the extent however to which parenchymatous degeneration or involvement of large blood vessels predominate as in paresis tabes primary optic atrophy Erb s paraplegia or focal vascular neurosyphilis the clinical results of treatment are limited by the pre existing amount of parenchymal damage because no treatment of any kind can repair destroyed nerve cells

Treatment Asymptomatic neurosyphilis in general responds well to treatment Proper treatment with adequate follow up and re treatment if indicated provides almost complete assurance against the subsequent development of clinical neurosyphilis Treatment is intended to render the spinal fluid inactive and if possible negative and to prevent the development of clinical disease

Penicillin therapy is the treatment of choice It exerts a prompt and dramatic effect on abnormalities in the cerebrospinal fluid The cell count usually returns to normal within ten to twenty four weeks after treatment and usually remains normal thereafter The protein content is reduced less promptly usually reaching normal by the sixth month The Wassermann and colloidal tests improve more slowly The rapidity and extent of the trend toward a normal spinal fluid is dependent on the degree of the abnormalities present before treatment and on the duration of infection more prompt and satisfactory response occurring in early than in late asymptomatic neurosyphilis

In asymptomatic neurosyphilis the results of penicillin therapy are superior to the best attainable by metal chemotherapy and equal to those attained by the far more hazardous expensive and unpleasant fever therapy Although the time dose relationship has not been clarified it seems preferable to use large rather than small doses If the patient is hospitalized aqueous penicillin may be given in a total dose of ten to twenty million units over a period of twelve to twenty one days This may be given as 150 000 units every six hours or 75 000 units every three hours For ambulatory treatment procaine penicillin with aluminum monostearate 600 000 units (2 cc) daily or every second day until a total of ten to twenty million units has been given is recommended Herxheimer reactions other than a febrile response are rare in asymptomatic neurosyphilis

Follow up

After the completion of treatment the spinal fluid should be re tested every six months for the first two to three years and at yearly intervals thereafter If the cell count and quantitative protein fall to normal and remain so regardless of the response of the spinal fluid complement fixation or colloidal curve the patient should be maintained under observation only If however there is recrudescence of activity as determined by pleocytosis or indubitable and confirmed increase in quantitative protein re treatment should be given The second course of treatment should be a repetition of the first

Acute Syphilitic Meningitis

This condition a manifestation of early neurosyphilis responds dramatically to penicillin therapy in a dosage and by a schedule identical with that for asymptomatic neurosyphilis Symptoms such as

because of its nontoxicity rather than its superior therapeutic effect Penicillin, locally, in 'strong ophthalmic ointments (100,000 units per Gm) or by iontophoresis, has been helpful in some cases but the risk of local sensitization has not yet been de fined Its use is not at present recom mended

Fever Therapy If there is no response to penicillin fever therapy may be tried—eight to twelve febrile paroxysms either from malaria or from typhoid vaccine Since there is no evidence that fever therapy is other than a nonspecific form of treatment in interstitial keratitis the lower tempera ture range of typhoid vaccine therapy is perhaps equally efficacious and less disturb ing to the patient than malaria therapy

ACTH and Cortisone Evidence has accumulated that the systemic administra tion of ACTH or cortisone exerts a bene ficial effect upon interstitial keratitis similar to that observed in other forms of uveitis and kerato uveitis Although relapse frequently occurs as soon as treatment is terminated it is believed that ACTH or cortisone therapy may serve to tide some patients over until spontaneous subsidence of the process ensues It has also been shown that cortisone administered topically often produces a dramatic response with marked clearing within forty eight hours The re sults in interstitial keratitis are however not as constant as with other acute anterior ocular inflammations One should employ either the ophthalmic suspension 25 mg per cc in which the vehicle is a buffered phosphate solution with 1 5000 benzal konium chloride (zephiran) as the pre servative and spreading agent or an oint ment in 25 mg per cc concentration

The suspension is utilized in doses of one drop every hour during the day and every two hours during the night The ointment is instilled every three hours during the day and every six hours during the night The lids are immobilized with a pad The interval between doses and the duration of treatment should be varied according to the progress of the case The best results are apparently obtained if treatment is begun early The present indications are that cortisone used locally will be an ex tremely valuable therapeutic agent in inter stitial keratitis At the present time the treatment of choice in acute cases would appear to be a combination of local corti sone and systemic administration of peni cillin

Re-treatment Relapses of interstitial keratitis after treatment should be re treated either with fever therapy plus peni cillin or preferably with ACTH or cortisone plus penicillin Great caution should be exercised in predicting the effect of treat ment to the patient or his family The scars of inactive interstitial keratitis do not respond to treatment which should be given only if the systemic infection has been pre viously inadequately treated Corneal trans plants are sometimes successful

Follow up Post treatment follow up of patients with ocular syphilis is similar to that for the appropriate state of the sys temic infection except for ophthalmologic observation of the local effects of treatment

NEUROSYPHILIS

Asymptomatic Neurosyphilis

Invasion of the nervous system occurs early in the course of the disease Usually it is when the secondary manifestations occur Except for the occasional occurrence of syphilitic meningitis, this asymptomatic neurosyphilis is recognizable only by routine examination of the cerebrospinal fluid The outcome of asymptomatic neurosyphilis is discussed subsequently It may remain asymptomatic or it may lead, usually after a period of years, to a com plex group of clinical syndromes which differ widely from each other in symptoms and in prognosis From the neuropathologic standpoint, meninges, blood vessels and

convulsive seizures anticonvulsant drugs (phenobarbital, 'dilantin) should be given before and during therapy

To summarize the situation in paresis The immediate effects of penicillin alone on the cerebrospinal fluid appear to be as good as those of penicillin plus fever therapy the immediate effects of penicillin on the clinical status are good but whether as good as penicillin plus fever therapy is unknown and the ultimate effects of penicillin alone are as yet not completely known On the other hand the dangers and expense of penicillin therapy are incomparably less and its availability to most patients incomparably greater Recommendations for treatment are based upon a consideration of all of the above factors

Treatment Fever therapy preferably with malaria should be combined with penicillin as the initial form of treatment for relatively young paretics and taboparetics (under the age of 55) provided after thorough study the general physical condition is found to be excellent It is recommended that penicillin therapy be deferred until the initial temperature elevation (which minimizes the Herxheimer reaction) A full course of fever therapy (forty to sixty hours over 104° F) is given if it is tolerated and is accompanied by ten to twenty million units of penicillin given concurrently over a period of twelve to twenty one days

For patients over the age of 55 years or in poor physical condition or where adequate facilities for expert care during fever therapy are not available penicillin should be given alone as the initial treatment A large dosage given over a relatively long period of time is advantageous and a total of ten to twenty million units over a minimum period of seventeen days is recommended This may be given as 150 000 to 300 000 units every six hours or 75 000 to 150 000 units every three hours For the treatment of paresis and taboparesis hospitalization is desirable for many reasons However, good results have been obtained in patients for whom hospitalization was unobtainable, by administering repository penicillin Under such circumstances procaine penicillin with aluminum monostearate 600 000 units (2 cc) daily or every second day until a total of ten to twenty million units has been given is recommended

Follow up Post treatment spinal fluid examinations are conducted as outlined for asymptomatic neurosyphilis In addition detailed neuropsychiatric re examination should be repeated and compared with pre treatment observations at least as often as every six months for the first two to three years and yearly thereafter Re treatment is not indicated for a persistently positive spinal fluid complement fixation or colloidal reaction but if cell count and/or protein remain elevated or if once normal either or both increase to abnormal levels a recrudescence of activity is probable and re treatment, preferably with fever and penicillin is indicated

What to do in case of good spinal fluid response coupled with poor or incomplete clinical response is at present a subject of debate As previously stated, destroyed nerve cells cannot be rebuilt, so if it is evident that paresis is of long duration (a year or more prior to treatment) particularly if the pre treatment spinal fluid was inactive further treatment is likely to be of little value Certainly under such circumstances, if re treatment is to be given a combination of penicillin and fever therapy should be used It is a present belief that striking further improvement is rarely evident after the re treatment of patients in this category On the other hand patients who improve clinically after the initial course of treatment and who subsequently suffer clinical relapse should be re treated irrespective of whether or not there is a concomitant spinal fluid relapse

headache, nausea, vomiting fever, stiff neck, coma, and convulsions disappear, as a rule, within seven days and papilledema subsides within one to four weeks Recovery from seventh nerve paralyses is almost uniformly complete occurring within a few days to six months Approximately half of the patients with deafness recover normal hearing and the other half have residual mild to severe deafness The salutary effect upon the spinal fluid is similar to, but often even more rapid than in asymptomatic neurosyphilis Spinal fluid relapse is unusual and clinical neurorecurrence after treatment has not been observed The Herxheimer reaction is not to be feared Post treatment follow up is conducted as outlined for asymptomatic neurosyphilis Re treatment if indicated should consist of penicillin alone Fever therapy no longer has any place in the treatment of acute syphilitic meningitis

Paresis and Taboparesis

There is no unanimity of opinion concerning the optimum method of treating paresis and taboparesis Expert opinion is divided as to the advisability of using penicillin alone or in combination with fever therapy All are agreed that in paresis and in taboparesis as in all other forms of neurosyphilis the effect of penicillin alone on the cerebrospinal fluid is profound Abnormal cell counts and/or total protein rapidly fall toward and usually reach normal within two to three months after treatment Complement fixation and colloidal curve follow the same trend but much more slowly This favorable effect of penicillin therapy on the cerebrospinal fluid has been well sustained

The clinical outcome in paresis and taboparesis is much more difficult to evaluate than is the cerebrospinal fluid outcome and there is correspondingly more difference of opinion concerning the relative merits of penicillin alone or combined with fever therapy It is probable that this difference of opinion will not be resolved until a large group of alternate cases is compared with respect to the two methods of treatment

It should be emphasized that the efficacy of penicillin alone is no longer in doubt, the question in point being only whether the addition of fever therapy results in greater and more sustained improvement in a larger percentage of patients Penicillin given alone is already known to extend the average four year life expectancy of the untreated patient and to improve the mental status in over half the cases Many patients have been returned to gainful occupations All observers agree that somatic symptoms (tremor speech and writing defects undernutrition) and brain wave abnormalities shown by the electroencephalogram are frequently and strikingly improved by penicillin alone This improvement is often manifest within a few weeks after treatment is completed

Herxheimer Reactions Clinical Herxheimer reactions from penicillin are relatively frequent and sometimes severe in paresis and cannot be avoided by the initiation of treatment with small doses Temporary exacerbation of the paretic process may result in acute mania hallucinatory or paranoid trends or status epilepticus Rapid and progressive paretic deterioration has been reported Manic expansive schizoid or paranoid trends may appear in patients in whom such psychotic manifestations were previously absent All of these untoward results have been previously noted after fever therapy That their frequency has been increased by the utilization of penicillin is uncertain but probable As a rule, with adequate general medical care, including sedation or anticonvulsant drugs as indicated and maintenance of fluid and nutritional balance, the temporary ill effects of the Herxheimer reaction can be successfully countered

In a paretic patient known to have

uncommon but ordinarily are not serious Exacerbation of bladder difficulties if they occur at all do so with much less frequency than during fever therapy

Complications Under certain circumstances supplemental measures assume equal importance with specific treatment *in the* management of tabes dorsalis The disease leads to malnutrition in some patients so the importance of a nutritious and well balanced diet cannot be overestimated

Particularly is this true of those most miserable patients who suffer from intractable *gastric crises* and who may thereby come to extreme degrees of malnutrition and dehydration The acute attack can best be treated by the administration of 1500 cc of 5 per cent glucose in sodium chloride solution by intravenous drip repeated as often as necessary together with adequate sedative doses of sodium phenobarbital given hypodermically Atropine seems sometimes to be of value Morphine demerol or methadon often give dramatic relief but should be used only as a last resort because of the grave dangers of addiction

Various *neurosurgical* procedures have been tried for gastric crises with only partial success These include rhizotomy bilateral upper cervical chordotomy sympathectomy and vagotomy At the present time these cannot be recommended with any assurance Prefrontal lobotomy has been tried in a few cases and is a procedure to be considered as a last resort where all specific therapy has failed In the occasional elderly tabetic with intractable gastric crises there is no alternative to chronic controlled narcotic administration

Lightning pains may usually be controlled with codeine and the ordinary analgesics but morphine or one of the other stronger narcotics may be necessary The patient with *tabetic ataxia* should be told repeatedly that this is due to loss of position sense and can be at least partially compensated for by utilization of visual sense The expert cooperation of a trained physiotherapist is essential and astounding results may sometimes be accomplished The patient must be willing to devote hours daily to graduated exercises (the Frankl system is best) and must be encouraged to persist even though discouraged by relatively slow progress

Management of the *tabetic bladder* is of grave concern since ascending urinary tract infection is a frequent complication of tabes dorsalis Patients should be instructed to empty the bladder with the aid of lower abdominal pressure every three hours by the clock If pyuria is present urine cultures if available should be obtained and appropriate therapy instituted (sulfonamide compounds mandelic acid streptomycin aureomycin terramycin chloramphenicol penicillin) If urine cultures are not available gantrisin aureomycin or chloramphenicol should be used as the drug of choice

Persistent incontinence and urinary tract infection despite the above measures necessitate urologic consultation Estimation of bladder capacity and residual urine tests of kidney function and intravenous pyelography usually are then indicated After careful urologic study transurethral prostatic resection even in the absence of true median bar hypertrophy is frequently indicated often with gratifying relief of symptoms Weakening the vesical neck by surgical means allows a weak detrusor muscle to empty the bladder more efficiently

The orthopedic management of *Charcot joints* is more important as far as the local lesion is concerned than is specific treatment and expert consultation should be obtained Details of orthopedic management are beyond the scope of this chapter It should be stated however that operative procedures are not as a rule indicated and

Paretic Psychosis There are several points of interest with regard to the response of the paretic psychosis to any form of treatment In general the longer the duration of symptoms the more incomplete is the clinical remission The clinical response also seems to be dependent in part upon the psychotic syndrome being in general least satisfactory in those patients with schizoid or paranoid trends Of the greatest interest is the observation that electro shock therapy affects the psychosis of general paresis Shock therapy may be given a trial in an adequately treated paretic with an inactive fluid but with persistent psychotic trends Needless to state this form of therapy should be attempted only by those familiar with its use

Tabes Dorsalis

In tabes dorsalis as in paresis opinion is divided concerning the relative merits of penicillin alone versus penicillin plus fever therapy The cerebrospinal fluid response to penicillin alone is profound as in other ypes of neurosyphilis Because of the er atic and unpredictable course of untreated abes dorsalis it is difficult to determine he influence of any form of treatment on e clinical course of this disease Sponta ous remission in untreated tabes dorsalis frequent though how frequent or how manent is unknown One sees all grada ns of severity from the so-called gallop tabes to spontaneous and complete st Some patients with clear-cut physi igns of tabes never develop any symp In others one symptom such as nating pains or gastric crises may t for decades without other develop Still others may become gradually with one new symptom after another ot arthropathies and mal perforante ppear after years of quiescence illin Data are not yet available to ne whether penicillin therapy will ntly arrest the tabetic process

Symptomatic improvement has been frequently noted Decrease in frequency and severity of lightning pains has been reported by about half the patients but is not always maintained Some improvement has been observed in subjective paresthesias Gastric crises are rarely relieved About half of those with ataxia have shown improvement in gait but this is particularly difficult to evaluate since a considerable degree of improvement in gait may occur as a result of re-education by appropriate physiotherapy Impotence and urinary disturbances rarely and Charcot joints and trophic ulcers never, have responded favorably to penicillin therapy

In tabes dorsalis there is almost complete lack of correlation between clinical progression and spinal fluid activity The most severe gastric crises lancinating pains and trophic disturbances are frequently seen in patients with a negative or an inactive pre treatment spinal fluid Such patients respond poorly to all forms of antisyphilitic treatment the best symptomatic results usually being obtained in patients with an active pre treatment spinal fluid which of course suggests a relatively active inflammatory process rather than an entirely burnt out degenerative one

In view of the almost completely unpredictable effect of any form of treatment on the clinical symptoms of tabes dorsalis penicillin alone is recommended because of its safety and freedom from toxicity as the initial form of treatment in all cases except those accompanied by primary optic atrophy (subsequently separately discussed) If the patient is hospitalized ten to twenty million units of aqueous penicillin may be given over a period of fifteen to twenty or more days as previously described Ambulatory treatment may be carried out with a similar total dose of procaine penicillin with aluminum monostearate Herxheimer reactions particularly in the form of exacerbation of lightning pains are not

the same ophthalmologist perform pre treatment and follow up examinations

Vascular Neurosyphilis

More or less pure vascular neurosyphilis depends upon the existence of a localized or widespread cerebral or spinal endarteritis Vascular neurosyphilis causes cerebral vascular accidents hemiplegias monoplegias paraplegias hemianopsias and subarachnoid hemorrhage This form of neurosyphilis must be differentiated from the so called Lissauer s type of paresis which often comes on abruptly with a focal vascular accident In purely vascular neurosyphilis the spinal fluid usually is of the inactive type and may be entirely negative an important differential point Much more frequently necessary and even more difficult is the differential diagnosis between focal vascular neurosyphilis and a cerebral vascular accident due to some other cause such as hypertension or arteriosclerosis Even though the spinal fluid may be entirely negative syphilitic patients under the age of 50 who suffer vascular accidents without other obvious cause should be treated for syphilis despite an obvious inability to establish an unequivocal etiologic diagnosis The ultimate results of any type of treatment are only fair Even in those patients who respond favorably some degree of residual weakness usually remains Further vascular accidents are frequent

Treatment The results after treatment with penicillin like those from metal chemotherapy have not been striking Ten to twenty million units of penicillin is recommended as the treatment of choice because of its low toxicity rather than because of any proved therapeutic efficacy Fever treatment is contraindicated Post treatment follow up is determined by the gravity of the patient s clinical status Re treatment should be given only for reactivation of the spinal fluid If the pre treatment spinal fluid was inactive follow up puncture can be deferred for one year and performed only biannually thereafter

Syphilis of the Spinal Cord

Syphilis of the spinal cord (aside from tabes dorsalis) may be purely vascular as in thrombosis of the spinal arteries purely degenerative as in Erb s spinal spastic paraplegia (lateral columns) or syphilitic *progressive muscular atrophy* (anterior horn cells) largely meningeal as in hypertrophic cervical pachymeningitis or arachnoiditis gummatous (presenting as a spinal cord tumor) or mixed as in meningomyelitis The differential diagnosis between these several forms of spinal cord syphilis and also between syphilis and spinal cord disease of other etiology (tumor multiple sclerosis amyotrophic lateral sclerosis and combined system disease) often is exceedingly difficult

The results of any form of treatment are successful in proportion to the meningeal (inflammatory) element present as usually mirrored by an active spinal fluid with pleocytosis and are uniformly poor in the purely vascular or parenchymatous types Penicillin like other forms of treatment has been disappointing in Erb s spastic paraplegia On the basis of equal therapeutic efficacy and low toxicity it is recommended as the treatment of choice for all forms of spinal cord syphilis in total dose of ten to twenty million units If thrombosis of the spinal arteries is suspected on the basis of rapid onset and complete paraplegia with a negative or inactive fluid little is to be expected from any form of treatment In chronic cases (particularly of vascular etiology) with complete paralysis of the lower extremities and sphincters bed sores may be very troublesome and death is frequently from ascending urinary tract infection Fever therapy is not indicated for any form of spinal cord syphilis

Follow up Re treatment with penicillin should be given for reactivation of the

may end disastrously The objectives of conservative treatment are reduction of pain and swelling and protection of the joint from damage incident to use An acute Charcot joint should be put at rest in a splint or cast and weight bearing forbidden A joint distended with fluid should be aspirated as necessary Carefully controlled local heat and exercise without weight bearing are indicated As the pain and swelling subside, the surgeon should prescribe a suitable support in order that the joint may be protected as much as possible The skin must be watched to guard against pressure sores

The development of *mal perforante* (perforating ulcer of the sole of the foot in tabetics) probably rests on the same mechanism as that of Charcot joints Surgical removal of the affected area is often necessary One such ulcer has been observed to heal dramatically after lumbar sympathectomy performed to increase the blood supply to the affected area

Follow up Post treatment follow up is conducted in the same manner as for paresis Re treatment with penicillin is indicated for persistent or recrudescent activity of the cerebrospinal fluid What to do in case of good spinal fluid response coupled with poor or incomplete clinical response is at present a subject of debate Particularly if the pre treatment spinal fluid was inactive further treatment may be often of little value but for the patient with intractable gastric crises or lightning pains re treatment with fever plus penicillin may bring about a prolonged remission of symptoms even after penicillin alone has failed to do so

Primary Optic Atrophy

Primary optic atrophy usually though not always associated with tabes dorsalis is (except for paresis) the most dreaded of all the manifestations of neurosyphilis It should be widely recognized that syphilis is by far the most common cause of primary optic atrophy and that primary optic atrophy sometimes may constitute, together with pupillary changes the only clinical evidence of neurosyphilis Its early recognition and hence most efficient treatment would be facilitated by the routine ophthalmoscopic and perimetric examination of all patients with neurosyphilis

At the present time, the picture is most discouraging as the majority of patients have already lost useful vision by the time they finally reach a competent treatment agency The course of the untreated disease is extremely variable The process almost always becomes bilateral soon after the onset of symptoms Blindness occurs in 25 per cent of untreated patients within one year, in 50 per cent within two years in 75 per cent within six years and in 90 per cent within twelve years after onset of symptoms Progression is quite slow in a few patients The effectiveness of penicillin in primary optic atrophy will therefore require years of observation for determination, and there is already sufficient information that it is by no means uniformly effective

On the other hand fever (malaria) therapy is of established value It is essential that fever treatment be given before useful vision has been lost as no form of treatment can bring about improvement in a blind patient Penicillin in dosage and schedule as for tabes dorsalis should be given concurrently

Follow-up Post treatment follow up is as for tabes and paresis with additional careful perimetry and visual acuity determinations by an ophthalmologist at least as often as every six months for the first three years and yearly thereafter Re treatment with fever and penicillin is indicated for persistent or recrudescent activity of the spinal fluid and also is recommended for indubitable clinical progression beyond the limits of chance variation at the hands of different examiners It is important to have

an isolated phenomenon and with a normal spinal fluid

As is true in all other forms of neuro syphilis the response to treatment is in proportion to the inflammatory element present usually dramatic when occurring *in association with* syphilitic meningitis occasionally showing some improvement when occurring with other evidences of late neurosyphilis and almost never showing *any improvement when occurring as an* isolated manifestation with a negative fluid in either congenital or late acquired syphilis

The literature on pre penicillin treat ment is almost completely valueless largely due to lack of audiometric control Peni cillin alone according to findings in a small group of carefully studied cases brings about dramatic improvement in the type associated with syphilitic meningitis and improves some of the cases associated with late neurosyphilis No improvement has *been noted in the type occurring as an* isolated phenomenon (either congenital or acquired) with penicillin or with any other type of treatment Apparent arrest of progression by treatment has been observed in all types but it is not known how to evaluate this in the absence of a control series and long term follow up since spon taneous arrest also is known to occur Since the results from penicillin therapy are as well documented and appear to be as good as the results of other more drastic forms of treatment it is recommended as the initial course of treatment for eighth nerve deafness of all types in the usual dose of ten to twenty million units

Follow up After treatment the usual clinical and cerebrospinal fluid follow up should be carried out with special emphasis on audiograms by a trained otologist at intervals of six months at most *until suffi* cient time has elapsed to be reasonably certain the process is arrested Thereafter audiometry should be performed at yearly intervals Re treatment *for cerebrospinal fluid* relapse alone should consist of a second course of penicillin If clinical progression occurs after the initial course of treatment, re treatment with a full course of fever therapy plus penicillin is recommended

TREATMENT OF THE SYPHILITIC PREGNANT WOMAN

A syphilitic pregnant woman, untreated has on the average only one chance in six of delivering a live healthy child However the longer she has had syphilis and the more treatment she has received prior to pregnancy, the less is the chance of infec tion of the child Congenital syphilis can be eliminated by the routine use of the serologic test for syphilis in all pregnant women and the adequate treatment of the syphilitic mother during pregnancy Re sults after metal chemotherapy in the past generally have been good but now are far *surpassed by those following penicillin* therapy In contrast to metal chemother apy, penicillin is equally effective in pro tecting the fetus regardless of the trimester of pregnancy in which treatment is given It is however, advisable to begin treat ment as soon as the diagnosis of syphilis is established

Penicillin probably can prevent almost all congenital syphilitic infections, because *most treatment failures thus far reported* are potentially preventable by earlier diag nosis and more careful follow up of syphilis during pregnancy These failures have consisted essentially of grossly diseased premature stillborn fetuses due almost cer tainly to delay in diagnosis which caused nonviability before treatment could be in stituted and the birth of syphilitic infants due to undetected infectious relapse in the *treated pregnant woman*

Despite earlier reports *there is no satis-* factory evidence that abortion actual or threatened is more frequent during peni

spinal fluid and for clinical relapse after initial improvement following the first course of treatment The value of re treatment solely because of incomplete clinical response in the absence of an active post treatment spinal fluid is dubious Post treatment follow up is as previously described for other forms of neurosyphilis

Meningovascular Neurosyphilis

This term is a catch basket diagnosis which should be utilized only when the clinical syndrome cannot be fitted into a more definite diagnostic category In present day practice it is largely used to indicate patients with pupillary abnormalities and/or reflex changes and/or cranial nerve palsies An occasional patient with multiple focal lesions of brain and cord (diffuse cerebrospinal syphilis) is also included in this category In many cases classified as meningovascular neurosyphilis there is an underlying parenchymatous element the clinical picture of which is not yet sufficiently complete to permit recognition as one of the definite parenchymatous clinical entities The treatment of this group of diverse clinical entities can hardly be discussed as a group

Convulsions

Convulsions due to neurosyphilis (other than those associated with meningitis or paresis) since they are usually due to a scar do not as a rule respond to any form of antisyphilitic treatment The spinal fluid in such cases is frequently negative After careful elimination of other causes of con-vulsive seizures particularly brain tumor anticonvulsant drugs (phenobarbital dilantin for grand mal tridione for petit mal) must be continued often indefinitely

Gumma

Gumma of the brain usually presents symptoms similar to those of a brain tumor with signs of increased intracranial pressure, and is almost always seen first by a neurosurgeon If the nature of the tumor is recognized by the surgeon, a decompression operation alone should be performed and antisyphilitic treatment instituted Even if seen first and recognized by the physician neurosurgical consultation and decompression seem advisable as the initial step since lumbar puncture is contraindicated in the presence of increased intracranial pressure

The remainder of this group of 'unclassified or diffuse meningovascular neurosyphilis usually have few or no symptoms Pupillary and reflex changes are not altered as a result of treatment though cranial nerve palsies and multiple focal lesions frequently clear especially if there is a large inflammatory element and an active spinal fluid

Treatment Penicillin is recommended as the treatment of choice in total doses of ten to twenty million units by the usual schedules as previously outlined Judged by its effect on the spinal fluid it is efficacious and its effect on clinical symptoms when such are present is as good as other forms of treatment Follow up is as previously outlined for other forms of neurosyphilis Re treatment with penicillin utilizing the initial schedule is indicated for persistent activity or reactivation of the spinal fluid, which is most unusual Re treatment is not usually indicated for incomplete clinical response but may be necessary under certain circumstances such as a cranial nerve palsy that has cleared and recurred even in the absence of spinal fluid relapse

Deafness

Eighth nerve deafness occurring in association with early syphilitic meningitis has been discussed previously In late acquired syphilis it may be associated with other evidence of neurosyphilis or may occur

further treated in any pregnancy in which she has a positive blood serologic test for syphilis in a quantitative titer of 16 or more dilution units

4 A woman who is an indubitable congenital syphilitic and who becomes pregnant does not require treatment for the sole purpose of protecting the fetus She should be treated during pregnancy only if prior treatment has been inadequate according to standards discussed in the section on the treatment of congenital syphilis (if third generation syphilis occurs at all it must be exceedingly rare)

5 If the physician does not feel qualified to decide if treatment is indicated during a given pregnancy an expert opinion should be secured or failing that, re treatment with penicillin should be given

TREATMENT OF PATIENT WITH CONGENITAL SYPHILIS

Diagnosis

The treatment of infantile (early) congenital syphilis should not be undertaken until a positive diagnosis can be made The apparently normal infant born of a syphilitic mother must be followed after birth for a minimum period of four months by means of frequently repeated physical inspections and quantitatively titered serologic tests preferably determined every two weeks About 40 per cent of normal ultimately nonsyphilitic infants born of seropositive mothers have a positive cord blood serologic test for syphilis and may remain seropositive due to the presence of maternal reagin for as long as three months after birth Conversely an infant with a negative cord serologic test for syphilis nevertheless may develop congenital syphilis later

The serologic test on cord blood obviously is worthless Similarly the histologic examination of the placenta may be discarded as valueless Moreover a wide variety of conditions in young infants may result in roentgenographic skeletal lesions closely simulating the changes due to syphilis Unequivocal osseous syphilis in the presence of negative serologic tests is rare and if it does occur, may actually be the residuum of a retrogressing treated intrauterine infection rather than an indication of active and progressive infantile syphilis The diagnosis of infection of the infant never should be made on roentgenograms alone, and this technic is not advised unless expert interpretation is available

A positive diagnosis of infantile congenital syphilis therefore must be based upon one or more of the following (1) a positive dark field examination of the wall of the umbilical vein (2) the presence of reagin in the infant s blood at the end of the third month of life, (3) the development of definite clinical signs of syphilis associated with a positive dark field examination or if the dark field is negative associated with a confirmed and definite rise in the titer of the serially quantitated serologic tests

Prognosis

Penicillin does not seem to lower the high mortality rate in infantile congenital syphilis much of which is due to intercurrent disease in these debilitated infants The consensus is that none of these deaths is due to the Herxheimer reaction The mortality rate is higher but the ultimate results of treatment in surviving infants are better in infants treated early at less than 3 months of age than in those treated at an older age The higher mortality rate in the younger group is doubtless because included are the more florid more easily diagnosed and more debilitated cases rather than due to the penicillin treatment per se Expressed differently, infants who have reached an age of 3 months untreated represent a selected group of survivors with the less florid and severe infections those untreated congenital syphilitic infants with the more severe infections having already died Dosage of penicillin

cillin treatment of the pregnant woman than during other forms of antisyphilitic treatment, nor indeed more frequent than the expected rate in normal women Also despite earlier suggestive evidence there is no statistically valid evidence that aqueous penicillin is superior to repository penicillin Indeed there is every theoretical reason to believe that it is not

It seems proper to begin treatment with a full dosage of penicillin and to treat with procaine penicillin on an ambulatory basis when hospitalization is not practicable Especially important in the treatment of the pregnant woman is prolonged sterilization of needle and syringe, because homologous serum jaundice during pregnancy is a particularly dreaded complication Fever therapy is of course contraindicated during pregnancy even if apparently indicated for the maternal disease The sole exception to this would seem to be the pregnant woman with rapidly advancing primary optic atrophy in whom the physician may decide to risk the life of the fetus in an attempt to prevent blindness in the mother

• Although there is general agreement that pencillin in dosage of 2 400 000 units is sufficient to prevent congenital syphilis this is not the optimal dosage for treatment of the mother For this reason standard courses of six to ten million units as recommended elsewhere in this discussion for the appropriate stage of the maternal infection should be used If labor seems imminent as much as 2 400 000 units of procaine penicillin may be given as the initial treatment preferably at multiple sites in the buttocks

Follow up

Following completion of penicillin treatment the pregnant woman should be followed clinically and with quantitatively titered serologic tests once a month until delivery A second course of penicillin similar to the first should be given if there is evidence of clinical or serologic relapse or in cases of maternal syphilis of less than one year's duration if the titer does not fall significantly within three months after treatment Re treatment during the same pregnancy need not be given to patients with late syphilis because of seroresistance alone

Recommendations for re treatment of the syphilitic pregnant woman who has been once treated prior to pregnancy are as follows

1 All pregnant women with syphilis of less than one year s duration should be re treated during pregnancy regardless of the amount of prior treatment and of an apparently satisfactory clinical and serologic status This is the critical period for relapse the lesions of which are often difficult to detect

2 Pregnant women with syphilis of more than one year s duration need not be re treated regardless of the stage and duration of syphilitic infection at the time of original diagnosis and treatment and regardless of the interval between the previous treatment and pregnancy provided that previous treatment has consisted of either 4 Gm or more arsphenamine (or its arsenical equivalent) with concomitant bismuth or 2 400 000 or more units of penicillin, and provided that the woman during the pregnancy in question shows no clinical signs of an active syphilitic infection and has either a negative or a low titer positive serologic test for syphilis (1 to 8 dilution units) Such pregnant women should be followed clinically and with quantitatively titered serologic test for syphilis monthly throughout pregnancy and treatment instituted in case of clinical or serologic relapse

3 Until data concerning the outcome of pregnancy in previously treated pregnant women with late acquired syphilis who retain high titer positive serologic tests is accumulated a syphilitic woman should be

fessional advice is sought with reference to *protection against possible future exposures*

In addition to the use of the condom which affords some degree of protection to both sexes male patients should be advised to use *local chemical prophylaxis im*mediately after exposure

The entire question of chemotherapeutic prophylaxis has been *re opened by the ad*vent of the almost completely nontoxic antibiotic penicillin For the treatment of rabbit syphilis this drug is approximately thirty two times more effective when given during the incubation period than when given for the established infection Moreover penicillin is capable of aborting syphilitic infection in man One study of the prophylactic treatment of 115 contacts of patients *with infectious early syphilis* demonstrated that only 6 of these contacts ultimately developed syphilis when they were treated at one visit with 900 000 units of penicillin in oil and wax 3 cc of bis*muth ethyl camphorate* and 0 05 to 0 06 Gm of oxophenarsine Even these 6 patients probably acquired the infection from a second exposure subsequent to treatment In contrast syphilis developed in 76 of 130 similar contacts who remained untreated

In view of the above clinical and experimental data the prophylactic treatment of the close repeater *contact (marital or* paramour) of all patients with primary or *secondary syphilis* is recommended This treatment should be given simultaneously with that given to the infected partner *both to prevent* the contact from developing clinical syphilis and to prevent reinfection in the original case Contact and patient may be given *identical courses of* treatment although a much smaller dosage would probably be effective for the contact Such contacts treated prophylactically should be followed clinically and serologically for a minimum period of six months and preferably for one year Prophylactic treatment for all casual sexual contacts of early syphilis is not yet recom*mended* because of relative lack of data as to the percentage of contacts who become infected as the result of a single exposure *to infectious syphilis*

For the patient who appears in the *physician s office requesting prophylaxis* several to twenty four hours after exposure to an unknown source it is permissible provided he is willing to remain under observation for six months to administer a single injection of 600 000 to 1 200 000 units of procaine penicillin with aluminum monostearate which will certainly protect against gonorrhea and *will* almost certainly protect against syphilis

For the physician or nurse who has inadvertently handled lesions of early syphilis soap and water, if immediately and *thoroughly applied to the hands provide* adequate prophylaxis If abrasions are present especially about the nails calomel ointment or soaps containing phenyl arsenoxides should be thoroughly rubbed into *the hands after washing Puncture wounds* from an infected needle recently used on a patient with early syphilis or on an animal with experimental syphilis are exceedingly dangerous because the organisms if present on the instrument are introduced deeply beneath the skin It seems preferable to take a full course of penicillin under these circumstances but some physicians or nurses might prefer careful clinical and serologic follow up over a three month period undergoing treatment only if lesions develop

is of less importance than age and general condition of the infant but total dosage of more than 40 000 units per kg body weight is more effective than total dosage of less than that amount Infants with congenital syphilis should be hospitalized and given expert supportive pediatric care (such as fluids for dehydration transfusion for anemia and restoration of electrolytes) concurrently with the immediate institution of penicillin in full dosage

Treatment

Although it has not been possible to assess accurately the increased value (if any) of larger dosage schedules current recommendations are for the administration of penicillin G in aqueous solution every three to six hours day and night in a total dosage of 100 000 to 400 000 units per kg of body weight over a period of eight to fifteen days Ambulatory therapy has not been satisfactorily developed for any considerable number of cases and is not advisable because of the necessity of adequate supportive measures

Because of the possible infectiousness of the breast milk of untreated or inadequately treated mothers with early syphilis an apparently healthy baby born of such a mother should be bottle fed from birth

Follow up

Post treatment follow up of infants with early congenital syphilis should in general consist of that already outlined for early acquired syphilis Spinal puncture should not be omitted The indications for re treatment are identical with those already discussed for early acquired syphilis Re treatment should be with penicillin alone preferably in twice the initial total dose and if feasible, over twice the initial period of time

Late Congenital Syphilis

It is unnecessary to offer details on the treatment of late congenital syphilis in infants over the age of two years children or adults The treatment of interstitial keratitis eighth nerve deafness and congenital neurosyphilis in general has already been discussed under the appropriate sections The stigmata of late congenital syphilis are irremediable Late latent benign late and hepatic congenital syphilis do not differ in their response to treatment from the corresponding stages of the acquired disease Cardiovascular lesions are almost nonexistent In children over the age of 6 years the tendency is to use adult dosage schedules whereas in younger infants the more or less standard total dose of 100 000 to 400 000 units per kg may be employed

Post treatment follow up and indications for re treatment are identical with those recommended for corresponding types of acquired syphilis Seroresistance often at a high level is the rule The importance of the differential diagnosis between late congenital syphilis and a biologic false positive serologic test for syphilis in the adult has already been discussed in the section on the interpretation of serologic tests

Prophylaxis

ERE are three types of prophylaxis hanical local chemical (which aims at ruction of treponemes before invasion) chemotherapeutic Mechanical prophylaxis by means of the condom is still the most practical of all prophylactic methods and is the method which should be recommended by the physician whose pro

tact may be made by the physician, the patient or a representative of the local *health department* Direct approach on the part of the physician in private practice is usually not feasible except under certain special circumstances Marital or family contacts and some extramarital contacts can best be approached by the patient himself while other extramarital contacts will have to be sought out by the health department

It is the responsibility of the private physician either to examine these contacts personally or to see that they are examined in the local health department clinic The patient will usually prefer to have family paramour steady girl friend or steady boy friend examined in the physician s office whereas casual contacts and prostitutes usually are best handled by referring them to the health department clinics

How best to explain the situation to the marital partner is a delicate matter which often calls for great tact and discrimination A recommended method is the round table discussion in the physician s office the keynotes of which are (1) avoidance of incrimination of either partner as the source of the infection (indeed this is often impossible even for the physician to ascertain) (2) preservation at all costs of the family unit, (3) emphasis on the numerous methods of transmission of the disease other than by sexual intercourse (4) avoidance of examination under some unrelated pretext and (5) clear understanding by both partners of all the problems involved in examination, treatment follow up and prognosis

Immunity

THERE is no indication of a true racial immunity to infection although racial variation *in the course of the disease* is well known It is not possible to assess accurately the degree to which natural immunity may occur in man That certain persons do possess a degree of resistance is indicated by recent studies in which approximately *50 per cent* of the sexual contacts of primary and secondary syphilis apparently escaped infection

Shortly after the onset of the primary lesion in man a local immunity develops which prevents the development of a new lesion following reinoculation This so called chancre immunity is relative only, because reinoculation with massive doses of organisms will result in a lesion The duration of this chancre immunity is questionable as several investigators have reported successful intracutaneous inoculation of patients with paresis and tabes It is highly probable that the longer the patient has had syphilis before therapy is given the more likely he is to be immune to reinoculation or to develop an asymptomatic rather than a symptomatic reinfection It is also highly probable that a considerable proportion of serologic relapses may actually represent asymptomatic reinfection

The relative immunity to reinfection in late syphilis is accompanied by an altered allergic like reaction state of the host to his own organisms because there is frequently marked destructive and inflammatory tissue response to the presence of relatively few organisms In other instances the host may be said to be anergic as the treponeme lives throughout the life time of the host without provoking any tissue reaction Many persons for causes unknown

Contact Investigation

IT IS the physician's responsibility to secure the cooperation of the syphilitic patient by explaining the disease to him in understandable terms and by discussing with him the reasons for treatment and for post treatment observation. Stress should be laid upon the method of transmission. The foundation is thus prepared for securing the examination of every person *known to have been exposed to the* disease during the period of infectiousness. Whether or not the physician will wish to undertake the contact investigation personally or to delegate it to the local public health authorities will depend upon the circumstances of the individual case, the interest and ability of the physician, and the attitude of the local health department in placing well trained contact investigators at the disposal of the private physician.

The following outline contains suggestions classified according to the diagnosis of the original patient to aid the physician in determining what contacts it is important to examine. For convenience, gonorrhea is also listed.

I Primary syphilis
  - A Marital partner or paramour
  - B All sexual contacts during the three months period prior to the appearance of the primary lesion
  - *C Household contacts only when the* patient has open exposed extragenital chancre and intimate relationship such as that of a young child to the parent exists

II Secondary syphilis (includes infectious and serologic relapse)
  - A Marital partner or paramour
  - B All sexual contacts during the six months period prior to onset of secondary lesions or of relapse
  - C Household contacts—proceed as under primary syphilis

III Early latent syphilis (known to be of less than one year's duration)
  - A Marital partner or paramour
  - B All sexual contacts extending back to six months prior to the appearance of lesions
  - C Children of female patients born since the patient became infected

IV Latent syphilis (duration more than one year or duration unknown) and late syphilis
  - A Marital partners or paramours, particularly if exposed at time of known or presumed infectious period of the disease
  - B All children of female patient

V Syphilis in pregnancy
  - A The infant
  - B Other contacts depending upon stage of maternal infection

VI Congenital syphilis
  - A All family contacts—father, mother and siblings

VII Gonorrhea
  - A Marital partner or paramour
  - B All other sexual contacts during two weeks period prior to onset of symptoms

Extramarital Contacts

Identification of marital and family contacts usually offers no problem, but identification of extramarital contacts may be difficult. If possible, the full name and address, marital status, and information on the home situation should be obtained. If not obtainable, nicknames, identifying physical characteristics, approximate age, place of work, usual hang out, place of meeting or of actual contact, and other descriptive data may be sufficient to permit identification. Actual approach to the con

Prognosis of Treated and Untreated Syphilis

Early Syphilis

If the patient has early syphilis he may be told that his chances for attaining real symptomatic and serologic cure with adequate treatment are approximately 80 to 90 per cent but he must also be told of the necessity of serologic and clinical follow up and of the possible necessity for re treatment After five years of negative follow up including a negative spinal fluid examination one year after conclusion of treatment he may be discharged as cured

Infantile Congenital Syphilis

Infantile congenital syphilis has a high mortality rate which is materially reduced but by no means eliminated by treatment Congenital neurosyphilis particularly juvenile paresis has a dire prognosis and responds poorly to treatment doubtless due to the advanced stage usually present before the disease is recognized Late congenital syphilis in other respects does not threaten life Cardiovascular involvement is almost unknown Permanent disability in such vital structures as the eye or ear is frequent

Late Latent Syphilis

If the patient has late latent syphilis he must be told that the serologic test for syphilis is not a criterion of cure and that its persistent positivity does not necessarily indicate persistence of infection He must not be told that treatment will render his blood test negative since this is most unlikely to occur He should be told that he is not now sick and that treatment is being given as a preventive measure His chances of remaining well after adequate treatment are about 90 to 95 per cent

Benign Late Mucocutaneous and Osseous Syphilis

In benign late mucocutaneous and osseous syphilis he may be assured of speedy symptomatic relief and of the same ultimate good prognosis as in latent syphilis though the likelihood of subsequent benign late lesions is greatly increased

Cardiovascular Syphilis

In cardiovascular syphilis (aortic regurgitation and aneurysm) discussion of cure had best be avoided as it is not attainable too much should not be promised of antisyphilitic treatment Instead the situation should be considered as any other form of heart disease after a careful evaluation in the individual patient of the degree of cardiac enlargement valvular damage myocardial insufficiency and aneurysmal dilatation The prognosis is not always gloomy Numerous patients with aortic insufficiency or aneurysm have been observed who have remained essentially asymptomatic over a period of many years

Ocular Syphilis

In ocular syphilis associated with early syphilis the prognosis for vision is usually excellent but in the interstitial keratitis of congenital syphilis and in late ocular lesions of acquired syphilis it is wise to promise nothing since the local response to therapy is completely unpredictable

Neurosyphilis

The prognosis in neurosyphilis is variable depending upon the duration of syphilis and the type of involvement This has been discussed in the section on its treatment The abnormal spinal fluids sometimes observed in untreated secondary syphilis have no unfavorable influence on

may change from anergic to the allergic state and vice versa

Immunity is probably more largely cellular than humoral Recently, however, the presence of humoral (serum) immobilizing and protective antibodies against *T pallidum* has been indubitably demonstrated Attempts at active and passive immunization against syphilis to the present time have proven uniformly fruitless

INFECTIOUSNESS OF UNTREATED AND TREATED SYPHILIS

The treponeme dies as soon as it dries It can pass from an infected to an uninfected person only by direct or close indirect contact of moist body surfaces—the genital and buccal mucous membranes Although the patient with early syphilis should be told of the possibility of infecting others by casual means it is reasonable to assure him that the real danger is by means of sexual intercourse or kissing In broad general terms it may be said that the mucosal and to a lesser extent the cutaneous lesions of early syphilis whether congenital or acquired are infectious and that the late lesions of syphilis even though they are moist are not infectious

Even in the absence of treatment the danger of direct transmission to others is inversely proportional to the duration of the disease in the patient Certainly after the fifth year the risk of infecting others even by sexual intercourse is remote and most patients even if untreated are noninfectious after two years of the disease by which time 85 per cent of infectious relapse has occurred

Under the influence of antisyphilitic treatment with arsenicals or penicillin the patient is for practical purposes nonin ectious twenty four hours after the initial njection After the termination of treat ent, however a small proportion of these tients undergo infectious relapse and ce again become a potential source of infection Most relapses after the intensive methods of treatment occu ing the first year Ideally therefore s intercourse and moist kissing shoul avoided for an entire year Since such vice is unrealistic, the physician must o accept a reasonable compromise such permitting intercourse with a condom a the first few months of post treatment servation

Infectiousness and the Serologic Test for Syphilis

It is essential to emphasize that there i no relationship whatsoever between the re sult of the serologic test for syphilis and infectiousness Seronegative primary syphi lis is highly infectious and untreated late syphilis in which the serologic test is almost always positive is not infectious Ignorance of this point by physicians and legislators has led to many discriminating practices including denial of employment and of the marriage license in many states

Infectiousness of Blood (Transfusion Syphilis) and Milk

The rapid increase in the popularity of blood banks and particularly the accumulation of large stores of plasma have made important the study of survival of *T pallidum* under these conditions Six days is the maximum time that *T pallidum* has been observed to survive in plasma or blood heavily seeded artificially even under optimum survival conditions The fewer organisms in stored human syphilitic plasma or blood minimize the risk of its infectivity so that for practical purposes blood or plasma stored under the usual blood bank conditions for ninety six hours may be assumed to be noninfectious The danger of transfusion syphilis appears to be eliminated entirely with the use of processed (frozen and dried) human plasma or serum containing not more than 1 per cent moisture

taneous cure The Rosahn figures based upon the autopsy findings in 198 untreated patients are similar Anatomic lesions of syphilis were found in 39 per cent of these patients and were absent in 61 per cent Only 23 per cent of the 198 patients died primarily as a result of syphilis

While the above data are subject to a number of valid criticisms the evidence at hand does indicate that in a large proportion of cases syphilis is a self limited disease, the treponeme either living in perfect symbiosis with the host, or succumbing to natural bodily defenses When it does kill or seriously maim, syphilis does so only after many years of infection This most important point should be indelibly imprinted upon the minds of those who treat syphilis, and the relative risks of the particular treatment contemplated should be weighed against the risk from the disease itself in the particular patient concerned

ltimate outcome after proper treatment Acute syphilitic meningitis responds well ı treatment both clinically and from the boratory standpoint, and in general a ood prognosis can be given

In asymptomatic neurosyphilis, the prog osis with penicillin treatment is excellent In late clinical (symptomatic) neuro yphilis, the gravity of the prognosis is di ectly proportional to the degree of paren hymal involvement In general, the rognosis for life in tabes dorsalis is excel nt but poor for symptomatic relief Prom ses should not be made, especially for astric crises, lightning pains, cord bladder mpotence, and Charcot joints In paresis, vith optimum treatment the prognosis is often excellent In general it is favorable n early paresis with relatively little dete ioration and unfavorable in late paresis vith advanced deterioration Approxi nately one third of paretics can be re habilitated, one third can be partially mproved, and one third will not be bene ited except that their life may be pro longed

In primary optic atrophy and eighth nerve deafness no amount of treatment can bring about real improvement though, with proper treatment arrest of the process can be expected in a significant proportion of cases In vascular neurosyphilis the prog nosis for function should be guarded and can best be determined after several months of post treatment observation In the vari ous syndromes of diffuse meningovascular neurosyphilis, the prognosis is on the average relatively good but there are so many exceptions that each case must be individualized after careful study and ob servation

Every patient with late syphilis must be examined periodically for the remainder of his life The intensity and type of follow up varies, but all patients should receive complete physical examinations every year or two

The physician who bases prognostic esti mates upon the results of serologic tests alone will find himself repeatedly in serious difficulties Although of considerable value in follow up of patients with early syphilis, serologic tests offer little in the prognostica tion of late syphilis Progression may occur despite negative serologic tests and, occa sionally, even with a negative cerebrospinal fluid On the other hand, many patients, treated or untreated, go through life with no evidence of infection except a positive s

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however, many such patients may be bio logically cured, as evidenced by reinfection or absence of lesions at autopsy

The influence of inadequate treatment upon prognosis varies according to the stage of the disease during which the treat ment is administered In early syphilis, a little treatment is often worse than none, whereas in late syphilis, this is probably not true because, early in the disease, the development of immunity may be pre vented by treatment If treatment is then prematurely terminated while foci of the organisms remain, the latter may multiply locally and also may undergo generalized redissemination On the other hand in late syphilis immunity is firmly established and is probably not impaired by treatment in any amount

Data concerning the prognosis of un treated syphilis are available from several sources The Bruusgaard figures based upon the clinical or pathologic follow up, three to forty years after infection, of 473 patients with untreated originally early syphilis indicate that, of every 100 patients acquiring syphilis, approximately 10 will ultimately develop clinical neurosyphilis, 13 cardiovascular syphilis 12 benign late mucocutaneous or osseous syphilis, and 65 will pass through life unharmed by the disease Approximately 28 will attain spon

essary, as the gram stained smear is satisfactory. Since the male is almost always the original patient, the embarrassment and trouble of securing the patient's sexual partners for treatment can be avoided if the physician can be certain that he is treating nonspecific urethritis and not gonorrhea. Moreover, nonspecific urethritis, which constitutes a substantial proportion of all nonpurulent urethral discharges, does not as a rule respond to penicillin therapy. In the absence of a urethral discharge, treatment should be preceded by culture of the first urine but may be given on adequate epidemiologic grounds if cultures are not available.

In women treatment on epidemiologic grounds is justified. All women who are sexual partners of males with proved gonorrhea should be treated without awaiting bacteriologic proof of diagnosis. Reliance on negative smears to rule out gonorrhea in the woman and failure to appreciate the epidemiologic approach constitute the most frequent sources of error in the management and control of gonorrhea. Observations in our own clinic indicate that cultures result in the detection of gonococci about three times as often as smears in specimens from the genitalia of untreated women suspected of having gonorrhea. Even cultures are not absolutely reliable. Mahoney has demonstrated this by securing second cervical cultures within six days in 237 women from whom positive cultures had been obtained previously and who had not received treatment in the interval. Only 73 per cent of the second series of cultures were positive. The ideal procedure is to take a cervical culture if facilities are available and treat the female contact on the same day.

Female children suspected of having gonococcal vulvovaginitis should first be subjected to cultures for diagnosis. Nongonococcal Neisserian vaginitis is frequent. Children who can be shown by culture to have true gonococcal vulvovaginitis should be subjected to contact investigation. A history of sexual exposure frequently can be obtained.

TREATMENT

A single intramuscular injection of 300 000 units of any type of procaine penicillin is recommended as the treatment of choice for uncomplicated gonorrhea in both sexes and all age groups. Its efficacy approaches 100 per cent. Indeed, where expense is a factor, as in clinic work, as little as 36 000 units (0.12 cc) has proved effective. Tablets of penicillin are also effective if given orally in adequate divided dosage. The total dosage should be three to five times that given by injection. Reports of penicillin resistant gonorrhea have been published, but we have seen none and Hughes and Carpenter, in an experience with 216 alleged cases of this type, adduced no such evidence. To date, strains of the gonococcus have not been observed to grow in vitro in a concentration of penicillin greater than 0.15 μg per cc of medium. Practically all, if not all failures can be ascribed either to erroneous diagnosis or to reinfection.

Follow-up

All patients treated with penicillin* for gonorrhea should be followed clinically and serologically once a month for at least four months to rule out a possible masked syphilitic infection. A sharp febrile reaction within twenty four hours after the treatment of gonorrhea with penicillin

* Patients previously sensitized to penicillin may be treated with aureomycin, chloramphenicol or terramycin. These antibiotics are significantly less active than penicillin against the gonococcus both in vitro and in the clinic and share with penicillin the disadvantage of possible suppression of signs of early syphilis. Three 1.0 Gm or six 0.5 Gm doses of any of these three antibiotics given at six hour intervals will effect cure of gonorrhea in most patients. Follow up is conducted in identical fashion as for penicillin treated patients.

40. Nonsyphilitic Venereal Diseases

Gonorrhea, Chancroid, Lymphogranuloma Venereum, and Granuloma Inguinale

RICHARD D HAHN
& JOSEPH EARLE MOORE

Gonorrhea

ALL gonococcal infections with the exception of ophthalmia neonatorum some instances of vulvovaginitis in young girls and an occasional accidental gonococcal ophthalmia in adults are the result of direct sexual contact In women the initial symptoms of gonorrhea are so mild as to go almost unnoticed and the presence of the disease is not usually suspected by either patient or physician until complications occur or a sexual partner is infected Such circumstances render the successful treatment of gonorrhea often impossible if the epidemiologic approach is neglected

In clinical practice many men have been seen with half a dozen acute gonococcal infections in as many months the result of repeated reinfections from a marital partner or regular paramour who has refused examination and treatment The situation has become so acute that treatment of the original patient has been refused unless the marital partner or regular paramour is treated simultaneously Failure to observe this rule will frequently result in unnecessary discomfort for the patient and in embarrassment for the physician when the patient returns with an apparent relapse This epidemiologic approach is the most important factor in the management of gonococcal infections

In women with infants in the neonatal period it is wise to examine and make cultures from the infants eyes as well as to undertake the usual investigation of sex partners In men the treatment of acute gonorrhea should be preceded by a bacteriologic diagnosis Cultures are not nec

with an urologist and local evacuation of pus in addition to penicillin therapy This should be given in dosages of 300,000 to 600 000 units daily until resolution has occurred, since it is difficult or impossible to be certain of the absence of secondary bacterial invaders which may be much less susceptible to penicillin than is the gono coccus Appropriate antibiotic or chemo therapy for such secondary invaders, if culturally identifiable should be given The treatment of urethral stricture follow ing an old healed gonococcal infection is purely local, and should be in the hands of the urologist

In Women Practically the only women who voluntarily seek treatment for gonor rhea are those with genital complications, which usually develop unless these women are treated in the acute stage In the female child with vulvovaginitis genital compli cations on the other hand, are rare Rectal involvement is common in women but is usually asymptomatic and requires no special treatment Abscess of the vulvo vaginal (Bartholin s) gland should be treated similarly to local abscesses in the man The danger of pelvic invasion by the gonococcus is present from the onset of the infection but seems to be greatest immediately following the menses Salpin gitis may subside leaving no permanent damage, or pyosalpinx and tubo ovarian abscesses may ensue Localized pelvic peri tonitis with adhesions to loops of bowel, omentum, and peritoneum may develop The uterus is frequently fixed in retrover sion by these adhesions, and occasionally there is a collection of pus behind the uterus extending downward into the cul de sac Generalized peritonitis and the upper abdominal peritonitis of Curtis are rare

The bacteriology of gonorrheal salpin gitis is not clear This complication as a rule does not now require operation, and it is difficult to ascertain the viability of the gonococcus in the pelvic viscera Cul tural studies of more than 200 fallopian tubes made over two decades ago by Davis revealed that it is seldom possible to obtain the gonococcus longer than two weeks after disappearance of fever and leukocytosis In 1946, Cohn and coworkers reported cul tural studies on 65 female surgical patients with acute or chronic adnexal disease Cul ture material was obtained at operation In 45 of these patients gonococci could not be demonstrated either preoperatively on the cervix or in the operative material Of the remaining 20, who had positive cul tures prior to operation, gonococci could be recovered from the adnexa of only 1 and this patient had a positive cervical culture at the time of operation

It is probable therefore, that acute gonococcal salpingitis is a self limited process, and that advanced changes in the pelvic viscera are due to repeated tubal reinfection, either from repeated sexual contact or from a persistent infection of the cervix It is likely that a single injec tion of 300 000 units of procaine penicillin will be sufficient to destroy all the gono cocci in the tubes as it does on the cervix Because of uncertainty concerning this point, and because of the possibility of mixed infections with gram negative bacilli penicillin has been administered over a period of several days and other antibiotics or sulfonamides given concurrently The duration of treatment is judged by the progress of the individual case

Adjuvant therapy, including bedrest fluids codeine and an ice cap as necessary for pain, low pressure hot douches and strict avoidance of sexual intercourse is advisable Surgery does not have a place in the treatment of acute gonococcal infec tions of the pelvis or peritoneal cavity, ex cept for the occasional drainage of a cul de sac abscess The treatment of the sequelae of gonococcal infection, such as painful fixed retroversion of the uterus

iggests the presence of concurrent early yphilis (Herxheimer effect) Patients with onorrhea who are known sexual contacts of primary or secondary syphilis and pa ients with visible lesions suggestive of early yphilis are best treated with streptomycin which has no effect on syphilis A single njection of 0 5 Gm is usually effective

Criteria of Cure in Men

After penicillin treatment of acute gon orrhea in men the urethral discharge al most always disappears within twenty four hours Not infrequently a thin watery clear morning drop which is bacteriologi cally negative for gonococci may persist for as long as a week It usually is not sig nificant Nonspecific urethritis and prosta titis not infrequently follow gonorrhea however and the patient should be warned of its possible occurrence This in some instances represents a flare up of a chronic nongonococcal prostatitis which existed prior to the acute gonococcal infection When gonococci reach the posterior urethra the prostate is almost always in fected Penicillin therapy cures the gono coccal infection but fails to cure the pre existing nongonococcal prostatitis which has been exacerbated by the gonococcal infection

If the urethral discharge promptly dis appears and the two glass urine test is clear (except for shreds in the first glass) one week after treatment further tests for cure are unnecessary We have never en countered a *penicillin* treated pat ent with a clear two-glass test who subsequently was demonstrated to be an asymptomatic carrier If on the other hand the urethral discharge does not disappear or if the two glass urine test remains cloudy (after the addition of acetic acid) further bacterio logic study of d scharge or first urine is essential Under such circumstances cul tures are of incomparably greater value than smears If the gonococcus can be demonstrated re treatment is in order but if as is usually the case cultures for the gonococcus are negative the treatment is that of nonspecific urethritis and prosta titis preferably at the hands of a urologist

Criteria of Cure in Women

After penicillin treatment of acute gon orrhea in women the only satisfactory tests for cure are repeated cervical cultures (vag inal cultures in the female child) Three cultures a few days apart are desirable If facilities for cultures are not available the best test for cure is absence of rein fection in the male sexual partner *Tricl o monas vaginalis* vaginitis not infrequently occurs after the cure of gonorrhea in women and may be a source of considerable con fusion easily resolved by demonstration of the causative organism

Complications

In Men The treatment of the compli cations of gonorrhea can most conveniently be discussed under the headings of local complications in the man local complica tions in the woman and extragenital syn dromes Avoidance of prostatic massage of sounding and of local therapy has reduced to the vanishing point local complications in the male An occasional instance of epi didymitis and vasitis is still seen in the patient who has neglected to seek treatment for several weeks and a few examples of sterile epididymitis occurring the day fol lowing penicillin therapy probably due to pre existing subclinical invasion have been observed The usual single dose of 300 000 units of procaine penicillin cures gono coccal epididymitis but the pain swelling and tenderness are frequently delayed in subsiding Adjuvant therapy with a day or two of bed rest an ice cap a suspensory and analgesics is advisable

Abscess of the prostate seminal vesicles parafrenal bulbourethral or urethral glands will usually require consultation

In addition intrathecal injection of 10 000 units of penicillin daily until the spinal fluid cultures have become negative is suggested

Keratosis blennorrhagica the only skin disease peculiar to gonorrhea is rare Its response to penicillin is uncertain as it is not clear whether the lesions are due to the presence of gonococci cutaneous hypersensitivity to the organism and its endotoxin or to a combination of both factors In only 17 of the 166 reported cases were organisms having the appearance of gonococci observed in tissue sections and in only one instance was the organism recovered by culture of the lesion In the few published case reports response to penicillin given in large dosage over a long period of time has not been uniformly good but a trial of such therapy is recommended after careful cultural studies

Since *iritis* associated with gonorrhea is not due to the presence of gonococci in the iris and since it does not present local distinguishing features that permit its differentiation from acute iritis of other origin the etiologic relationship is not clear (compare with the uveitis associated with late syphilis) After cure of co-existing genital gonorrhea further treatment should be placed in the hands of the ophthalmologist.

Gonococcal *ophthalmia neonatorum* (and gonococcal ophthalmia in adults) is due to the actual presence of gonococci in the involved tissues and therefore responds dramatically to penicillin therapy Its incidence, of course, has been greatly reduced through the routine use of 1-2 per cent silver nitrate in the eyes of infants at birth a measure almost universally required by law Recent studies suggest that local or systemic use of penicillin is of equal prophylactic value The greater likelihood of sensitization from topical use suggests that systemic administration is preferable A single intramuscular injection of 30 000–50 000 units of aqueous penicillin G should prove adequate prophylaxis against ophthalmia neonatorum For treatment of the established infection in the infant 10 000 units of aqueous crystalline penicillin G should be administered intramuscularly every three hours and continued for twenty four hours after clinical recovery and until at least three negative cultures have been secured Topical penicillin is unnecessary In adults with gonococcal ophthalmia 600 000 units should be given daily until the same criteria of cure have been met

PROPHYLAXIS

The condom is a reasonably effective prophylactic against gonorrhea Local chemical prophylaxis is of doubtful value There is some evidence that a single oral dose of 500 000 units of crystalline penicillin G is effective Such a dose would probably be insufficient to mask syphilis and prolonged serologic follow up would not be essential If there has been known exposure to infectious syphilis a larger dose should be used *

* See also Chapter 39

Chancroid

CHANCROID is an acute localized disease of venereal origin caused by *Hemophilus ducreyi* a small short gram negative bacillus with rounded ends and tendency to occur in chains Usually the disease is self limited but in particularly unhygienic patients especially when the lesion is under a phimotic foreskin or about the clitoris where it cannot be properly exposed relatively prolonged disability and tissue de

hesions with symptoms persistent uterine eding giant hydrosalpinx, or tubo arian cysts rare instances of persistent bo ovarian abscesses and sterility is be nd the scope of this chapter and should st in the hands of a gynecologic surgeon

Extragenital Complications The extra nital complications of gonorrhea may be vided into two groups those due to the esence of the gonococcus in the involved sues and those in which the (usually peated) genital gonococcal infections pparently stir up processes elsewhere in he body which may be perpetuated by eans of some poorly understood mecha ism long after bacteriologic cure of the nital infection Favorable response to enicillin therapy in the former group onococcal arthritis and tenosynovitis onococcal ophthalmia gonococcal endo arditis and gonococcal meningitis) is to e anticipated but in the latter group heumatoid type of arthritis associated ith gonorrhea iritis associated with gon rrhea) the value of penicillin therapy is ncertain

True *gonococcal arthritis** is becoming xceedingly uncommon Most cases occur within four weeks of the onset of acute onorrhea The longer the delay between nset of genital infection and the arthritis he less likelihood is there of a true gono occal involvement

Isolation of gonococci by culture from an involved joint indubitably establishes the diagnosis but this is possible only in about 30 per cent of clinically diagnosed cases Lack of bacteriologic proof should not interfere with prompt treatment when acute usually monoarticular arthritis with or without tenosynovitis accompanies or shortly follows genital gonorrhea Such cases have responded well to penicillin in doses of 600 000 units intramuscularly daily for at least five days supplemented by aqueous crystalline penicillin G intra articularly in the case of readily accessible joints such as knee or ankle If repository penicillin is used intramuscularly, it is ad visable to give one or more priming intra muscular doses of 200,000 to 300 000 units of aqueous crystalline penicillin G

It is not clear whether intra articular injection of penicillin is really an essential part of the treatment but it does serve to maintain a high local concentration Fluid aspirated twenty two hours after the local instillation of penicillin into joint cavities has been demonstrated to contain appre ciable amounts of the drug One or two intra articular injections of 50 000 to 100 000 units each at twenty four–hour inter vals have usually been sufficient

The rheumatoid like, much less acute often polyarticular arthritis which often comes after the genital gonorrhea is cured, and which is seen particularly in men who have had repeated gonococcal infections has never in our experience responded to penicillin therapy, regardless of dosage or duration of treatment The management is that of rheumatoid arthritis from which indeed the differential diagnosis is often difficult or impossible

Though gonococcal *endocarditis** for merly ended in death there is reason to expect a favorable response to prolonged and intensive penicillin therapy as for other forms of endocarditis Aqueous penicillin G should be given every three hours around the clock in a total daily dose of 10 000 000 units and should be continued for a minimum of six weeks even though blood cultures have become negative and the clinical course is favorable

For the treatment of gonococcal *menin gitis*† systemic treatment with penicillin in a dosage comparable to that recom mended for endocarditis is advised con tinued for at least one week after clinical recovery and negative spinal fluid cultures

* See also Chapter 26

* See also Chapter 10

† See also Chapter 20

evidenced by the positive intradermal reaction and positive complement fixation test with Frei antigen and by changes in the serum proteins with hyperglobulinemia The filtrable agent which causes lymphogranuloma venereum is closely related to those which produce trachoma, inclusion conjunctivitis psittacosis, mouse pneumonitis, and certain atypical pneumonias They are probably not true viruses, in the usual sense of the word for two reasons all produce inclusion bodies which stain readily with aniline dyes and are visible with the ordinary microscope and the agents of lymphogranuloma venereum, trachoma, mouse pneumonitis and inclusion conjunctivitis are susceptible to the sulfonamides These properties are unique among viruses The lymphogranuloma venereum virus has been successfully grown on the chorioallantoic membranes and in the yolk sac of the chick embryo and is now available commercially (lygranum') for use in skin testing and in a complement fixation test

Many clinical syndromes are attributed to the virus of lymphogranuloma venereum, largely on the basis of a positive Frei test, or a positive reverse Frei test in known reactors Isolation and identification of the virus should be required before accepting a causal relationship between the presenting clinical syndrome and the lymphogranuloma venereum virus unless the syndrome is one in which the virus has previously been isolated Identification of the lymphogranuloma venereum virus after isolation is exceedingly difficult and requires an expert virologist

The proved manifestations of lymphogranuloma venereum in which the virus has certainly or probably been isolated are genital lesions inguinal buboes elephantiasis of the external genitalia proctitis and/or rectal stricture, meningitis follicular conjunctivitis urethritis and cervicitis It is probable that lymphogranuloma venereum may also be responsible for some instances of ulcerative colitis and rheumatoid arthritis Some other syndromes attributed to lymphogranuloma venereum include uveitis keratoconjunctivitis, various changes in the fundus oculi, chronic salpingitis, regional enteritis, pharyngitis and glossitis among sexual perverts, various skin lesions, purulent arthritis bladder lesions axillary adenitis following finger inoculation, and cervical adenitis following oral inoculation In laboratory workers septic fever, chills, sweats, articular rheumatism and cervical adenitis have been reported Malignant neoplasia in chronic genital or rectal lymphogranuloma venereum also has been reported

TREATMENT

The general principles of chemotherapy are essentially the same regardless of the presenting clinical manifestations of the disease Prior to the introduction of the sulfonamides various procedures were utilized with varying degrees of success These are now of historic interest only Topical applications, nonspecific protein therapy, immune transfusions intravenous vaccine therapy, and antimony compounds have all proved to be of little value After ten years of experience with the sulfonamides all observers agree that these drugs are of great clinical value, despite the fact that experimentally in mice these drugs do not always achieve a real cure,' that is they do not cause sterilization of the tissues

For the most part the evanescent initial genital lesion does not present a therapeutic problem, except for the necessity of repeated dark field examinations and of serologic follow up to rule out syphilitic infection The inguinal buboes of lymphogranuloma venereum respond well to sulfadiazine or sulfathiazole* in doses of 4 Gm

* Limited experience with gantrisin and with the sulfonamide mixtures suggests that they are equally effective

ruction may ensue Suppurative inguinal denopathy is the rule Systemic manifesta ons other than fever and a positive intra ermal test to the bacterial antigen are nknown

REATMENT

The sulfonamides are the treatment of hoice Sulfathiazole or sulfadiazine* is sually employed in doses of 4 Gm daily or a period of five to seven days Occasion lly a second course is required Local leanliness is of great importance with enerous use of soap and water supple nented sometimes by the local use of a owdered sulfonamide and by soaks of 5000 potassium permanganate Subpre utial permanganate irrigations are fre quently of value in the presence of hhimosis A dorsal slit is only rarely neces ary Local therapy should be avoided until epeated dark field examinations to rule out syphilis have been performed After administration of sulfonamides, painful wollen inguinal nodes frequently subside before fluctuation occurs If however there s definite softening aspiration should be performed Such buboes should never be ncised as a persistent draining sinus not nfrequently ensues

Penicillin is of little or no practical value in the treatment of chancroid Strepto mycin has been successfully employed in a dosage of 1 Gm daily for seven to twenty five days Little investigative work has as yet been done with the newer antibiotics Both aureomycin and chloramphenicol in doses of 0 5 Gm four times daily for ten days seem to be effective However just as with penicillin both drugs are capable of masking the signs of early syphilis and should be reserved for patients intolerant of the sulfonamides or for the rare re sistant case An integral part of the man agement of all patients with chancroid consists of serologic follow up for a period of three months to rule out concurrent syphilitic infection

* Limited experience with gantrisin and with he sulfonamide mixtures suggests that they are equally effective

PROPHYLAXIS

The condom is the most practical pro phylactic against chancroid Soap and water calomel ointment silver picrate ointment and mild silver protein are prob ably of little value in the prevention of this disease The local use of sulfathiazole ointment soon after exposure is probably of value Oral sulfonamides in large doses (5–7 Gm) for one or two days are of defi nite preventative value but are not advis able for routine use Aureomycin chlor amphenicol and terramycin are worthy of trial

Lymphogranuloma Venereum

LYMPHOGRANULOMA venereum* is a virus disease which is usually transmitted by sexual intercourse Although it is pri marily a disease of the lymphatics and lymph nodes its clinical manifestations are protean There may be acute or chronic tissue changes constitutional symptoms or clinical latency If the Frei intradermal test is to be accepted as specific the disease is widespread with natural tendency to spon taneous clinical cure It seems probable that generalization of the virus is the rule, as

* Other names frequently found in the literature include tropical bubo strumous or scrofulous bubo lymphogranuloma inguinale poradenitis venereal lymphogranuloma esthiomene lympho pathia venereum lupus vulvae chronic elephanti as s with vulvar ulceration inflammatory stricture of the rectum Nicolas Favre disease fourth vene real disease sixth venereal disease

doses of ferrous sulfate or ferrous gluconate, but transfusions are necessary at times A low residue high caloric high vitamin diet with vitamin supplements in therapeutic doses is recommended On several occa sions unmistakable evidences of nicotinic acid deficiency and ariboflavinosis have been seen in these patients The stools should be kept soft with mineral oil or a psyllium seed preparation

Massive rectal hemorrhage may occur and is an indication for immediate hospi talization Temporary or permanent colos tomy is sometimes necessary The occasional instance of ulcerative colitis thought to be due to lymphogranuloma venereum should be managed according to the general prin ciples governing the treatment of ulcerative colitis and should also be given the benefits of specific therapy

Miscellaneous

The successful use of sulfonamides for ophthalmitis due to lymphogranuloma venereum has been reported Buboes fol lowing extragenital inoculation should be treated according to the principles outlined for the treatment of inguinal buboes Few data are available concerning sulfonamide treatment of the other known or presumed manifestations of lymphogranuloma vene reum One probable case of diffuse oral in volvement responded well Certainly where the preponderance of evidence points to a lymphogranulomatous etiology a trial of chemotherapy is justified

Aureomycin

Although preliminary reports that aureomycin would be the trea choice for all manifestations of granuloma venereum, further inves has tempered early enthusiasm It clear that while aureomycin sometim a beneficial effect on the course of th ease, the response is slow and by no r uniform Its effectiveness appears to b the same order as that of the sulfonam A course of treatment with 20 Gm of au mycin administered over a ten day per constitutes a reasonable therapeutic tr for the early manifestations of the disea Ulcers of late lymphogranuloma venereur rectal strictures with proctitis and othe late manifestations cannot be expected to respond rapidly and therapeutic trial should consist of 70–100 Gm given over a period of thirty five to fifty days Chlor amphenicol is apparently less effective than aureomycin and terramycin has been too recently introduced for proper evaluation The sulfonamides remain the drug of choice for routine use

PROPHYLAXIS

Little is known concerning the prophy laxis of lymphogranuloma venereum but it is reasonable to believe that the condom is efficacious In case of known unprotected exposure, chemotherapeutic prophylaxis with the sulfonamides or aureomycin should be tried Local chemical prophy laxis against this disease is of undeter mined value

Granuloma Inguinale

RANULOMA inguinale is a granuloma is process due to *Donovania granulo tis* The consensus is that this organism merly thought to be a protozoan is a bacterium Although the disease is usually localized to the genital or inguinal regions extragenital and even generalized infec tion may occur Granuloma inguinale is

daily Constitutional symptoms (chills, fever, general malaise) disappear usually within twenty four to forty eight hours Within the same period local pain greatly diminishes In many patients suppuration is entirely prevented if treatment is begun sufficiently early Suppuration once begun will usually not recede however, and severe tension should be relieved by aspiration, which will usually not have to be repeated if the sulfonamides are continued Incision and excision should be strictly avoided be cause either of these procedures results, as a rule, in a draining sinus which may per sist for months

The optimum duration of treatment is difficult to determine Studies by Heyman indicate that the virus usually disappears from the buboes after 40 Gm of drug have been given, although in one case the virus was recovered from an excised bubo after four months of treatment with a total of 120 Gm of drug Therefore it is essential to administer treatment for two to three weeks

Elephantiasis of External Genitalia

In elephantiasis of the external genitalia due to lymphogranuloma venereum the results of sulfonamide therapy are usually not striking It nevertheless seems desirable to institute treatment for several months preliminary to plastic surgical repair in an attempt to reduce thickening and indura tion and to heal ulcerations

Anorectal Lymphogranuloma Venereum

The results of sulfonamide therapy in anorectal lymphogranuloma venereum are proportional to the degree of inflammatory proctitis present In proctitis without stric ture, the sulfonamides usually induce heal ing Symptomatic relief occurs promptly as a rule and is more or less complete within five or six weeks, with reduction in muco purulent and hemorrhagic discharge in crease in appetite, and gain in weight If proctitis is associated with stricture, the usual procedure is to prolong sulfonamide treatment for many months, often with rest periods At the Johns Hopkins Hos pital rectal clinic some cases have been treated as long as two years

Succinylsulfathiazole and Phthalylsulfa thiazole are particularly suited for use over a long period of time Both are relatively nontoxic and poorly absorbed from the intestinal tract, an average of only 5 per cent of the ingested drug being excreted by the kidneys High local concentration is produced The total daily dose of suc cinylsulfathiazole is 0 25 Gm per Kg body weight (15 Gm for an average adult) It is advantageous to give about half the total daily dose in divided doses by mouth at four to six hour intervals and the other half in powder form suspended in 60 cc of water as a retention enema The total daily dose of phthalylsulfathiazole is 3–7 Gm which may be similarly divided

The results of treatment are difficult to evaluate but are generally favorable Al though scar tissue does not resolve, enlarge ment of the rectal opening may occur because of diminution of marginal gran ulation tissue Rectal dilatations usually at weekly intervals, are as a rule also neces sary during the period of drug therapy Rectal diathermy also has been recom mended as a supplementary procedure, but some clinical results have been disappoint ing An old inactive rectal stricture with out concurrent proctitis cannot be expected to respond to any form of chemotherapy nor to the tocopherols

Patients with chronic lymphogranuloma venereum proctitis and rectal stricture are not infrequently chronically debilitated sometimes even gravely ill and they may lose a great deal of weight Severe anemia is the rule often of the microcytic hypo chromic type due to chronic blood loss This anemia usually responds well to large

loma inguinale although at the present time they appear to be slightly less effective than chloramphenicol The usual dosage is the same as with chloramphenicol Relapses which occur after either aureomycin or terramycin usually respond to a second course of treatment

Nothing definite is known concerning the prophylaxis of granuloma inguinale Apparently it cannot be classed with the other venereal diseases with respect to infectiousness, and is difficult to transmit even under the most favorable conditions

The newer antibiotics, aureomycin, chloramphenicol and terramycin open new vistas for the prophylaxis of all the venereal diseases, since these drugs taken orally are known to influence syphilis gonorrhea chancroid, granuloma inguinale, and to a lesser extent lymphogranuloma venereum Though systematic large scale studies concerning their prophylactic value have not yet been undertaken, they should prove exceedingly useful, especially under military conditions and in those areas of the world where chancroid, granuloma inguinale, and lymphogranuloma venereum are endemic Penicillin remains the drug of choice for prophylaxis against syphilis and gonorrhea alone

n extremely chronic disease which leads ltimately, in many instances, to severe ebility ending in extreme cachexia and ven death The process is often well ad anced when the patient first presents him elf for treatment Patients with advanced ranuloma inguinale require good general nedical care and often need hospitalization There is usually a profound anemia, often f the microcytic hypochromic type, which esponds well as a rule to large doses of errous sulfate or ferrous gluconate At imes transfusions are advisable A high aloric high vitamin diet with vitamin upplements in therapeutic doses is recom nended

TREATMENT

Antimony Compounds

Antimony compounds have been used for many years with indifferent success in the treatment of this disease Their effectiveness decreases in direct proportion to the dura tion and extent of the lesions The healing effect is slow and ordinarily requires weeks and even months of therapy Secondarily infected lesions respond especially slowly or not at all Chemoresistance may occur also even in early relatively clean lesions but this is much less frequent Relapse is frequent even after apparently complete epithelialization Indeed completely epi thelialized lesions may still show Donovan bodies on tissue section Treatment of granuloma inguinale with antimony is no longer recommended

Antibiotics

Neither penicillin nor the sulfonamides have any effect upon granuloma inguinale but penicillin is sometimes a useful adjunct when a secondary infection has occurred Superimposed fusospirochetal infection is a clear cut indication for the use of peni cillin The application of a 20 per cent suspension of podophyllin in olive oil to recalcitrant lesions is of some value as a supplementary procedure to antimonial therapy

Other local measures which aid in rid ding the ulcers of secondary infection in clude hot sitz baths, potassium permanga nate compresses, and daily cleansing of the lesions with hydrogen peroxide The surgi cal excision of accessible lesions has been successfully practiced, but should always be preceded and followed by specific antibiotic therapy Radiation therapy as an adjunct to chemotherapy has been rather extensively employed Since the introduction of the newer antibiotics, all of these procedures except local cleanliness are usually super fluous

Granuloma inguinale responds well to streptomycin, aureomycin, chloramphen icol and terramycin The usual dose of streptomycin is 1 Gm every six hours Al though a five day schedule will cure a high percentage of patients especially those with small lesions, chronic and extensive lesions usually require ten to fifteen days of treat ment Relapses after treatment with strep tomycin are not infrequent and often fail to respond to a second course of the anti biotic

At the present time chloramphenicol is the drug of choice for the treatment of granuloma inguinale The usual dose is 0 5 Gm by mouth every six hours for ten to twelve days Chronic and extensive lesions may require prolongation of treatment for twenty to thirty days A method of treating granuloma inguinale by intramuscular in jections has been recently described Excel lent results were obtained with a total of only three injections of 4 Gm each at seventy two– or ninety six–hour intervals Relapses after chloramphenicol are ap-parently less frequent than after strepto mycin therapy and such relapses as do occur almost always respond to a second course of treatment with chloramphenicol

Aureomycin or terramycin are also recommended for the treatment of granu

ditions in a normally degenerating body, not diseases such as occur in maturity complicated by degenerations

3 The object of treatment of disease in this group is to restore the diseased organ or tissue to a state normal to its age, not to an approximation of the state normal in maturity

Life Expectancy

AVERAGE age expectancy at birth in the time of the Stone Age was 18 years In the era of the Roman Empire it was about 20 to 30 years and by the Golden Age in England it had risen to 33 years At the time of the American Revolution, only two years had been added to the average span The curve of increased life expectancy then became steeper so that in the middle of the nineteenth century, average life duration was 40 years and by the beginning of the twentieth century, 50 years After the first World War life expectancy rose to an average age of 55 and after the second almost another ten years had been added A female born in the middle of the current century has a life expectancy at birth exceeding seventy years A comparison of the proportions of the various age groups in the population at this time, however, shows little change from 1750 Despite increases in the total numbers of people and the lengthening average life expectancy, there has been no notable increase in the percentage of septuagenarians, octogenarians, and nonagenarians

The changes in the population age have occurred primarily in the younger fraction The diseases which curtailed life in the higher years a century ago are just as lethal today but affect more individuals simply because greater numbers attain old age (Table 54)

The changed character of the population's aging pattern is due to many influences Among these are heredity, environment, improved social organization extension of better medical care, and development of specific remedies Methods of reducing obstetric hazards combined with better infant management and application of all measures through the developmental years are reflected in later decades Each influence has its value—better water, nutrition, housing, sanitation laws, public education, and others Their integration creates the environment for longer and healthier living

TABLE 54 FORECASTS OF POPULATION OF UNITED STATES, 1945–1975

Year	*All ages*	*Under 5 years*	*5–19 years*	*20–44 years*	*45–64 years*	*65 years and over*
1900	100.0	12.1	32.3	37.8	13.7	4.1
1945	100.0	9.4	24.1	38.8	20.4	7.2
1950*	100.0	8.3	24.6	38.3	21.1	7.7
1975*	100.0	6.8	21.4	36.1	24.7	10.9

* Forecast assuming medium fertility medium mortality, and no immigration.

Prepared by P K Whelpton assisted by Hope T Eldridge and Jacob S Siegel (U S Department of Commerce Bureau of the Census Washington D C 1947)

41. Geriatrics

JOSEPH T FREEMAN
& EDWARD L BORTZ

EFINITIONS of terms used in the study f the older age groups will aid in under anding the biologic clinical and socio ɔgic needs of the aging process

Gerontology (*geron* an old man and ɔgos the word or the science of) is a branch f biology dealing with the study of aging rocesses in all living organisms

Geriatrics (*geras* old age and *iatrikos* he medical care of) is the clinical science hich includes the diagnosis treatment nd general medical supervision of the older atient

Gerocomy or gerocomica (*geras* old age nd *komein* the nursing care of) is an old erm rarely used now Its earlier meaning vas the nursing care of the older patient out now it has taken on a wider interpre ation to include all the medical economic ɔolitical and social aids available for ipplication to the expanding problems of ige

Senility is the terminal stage of life in which the maintenance of physiologic balance is made more difficult by serious mpairment of physical and mental capa bilities It is not synonymous with geri atrics It is a vegetative and troublesome period in which every member of the family or family substitute agency must be used to ease the withdrawal from life The prime responsibility is not solely that of physicians although their part in this gerontologic phase is important

These definitions should not suggest the need for another specialty If anything at present effort should be made to avoid such a designation There is however a need to investigate the clinical patterns of the aging process and to elaborate procedures of treatment Possibly the geriatrist or geri atrician will emerge eventually on the medical scene as a result of the increasing scope of specialized knowledge but today too many gaps in knowledge exist to war rant a specialty Awareness of the results of the special studies among all physicians is needed so that all older patients rather than a limited few may benefit

The lengthy history of this science should not be overlooked since present interest can derive humility from generations of previous effort Nascher coined the word *Geriatrics* in 1909 and attempted to place the study on a scientific basis Three tenets paraphrased from his text were the bases of his philosophy of the study of older age

1 Older age is a physiologic entity like childhood not a pathogenic state of maturity
2 Diseases in older age are pathologic con

Theories of Aging

MANY causes have been proposed to explain the aging of tissues, organs, and organisms Some of these theories have had such popular acceptance as to modify temporarily the habits of large fractions of the population even though the concept was completely hypothetical and more often than not completely subjective A brief summary of some of these theories is derived from Nascher and other sources

The theory of Demange senile changes are due to 'a change in the quantity and quality of the interstitial nutritive material due to changes in the circulation and this is due to atheroma and arteriosclerosis

The theory of Thoma ceaseless activity of the heart and blood vessels gradually weakens the elastic fibers of the vessels The loss of tone permits a dilatation of the vessels the circulation is slackened and the nutrition of the organism is thus impaired

Durand Fardel postulated a vital principle of limited duration similar to the "élan vital of Bergson

Metchnikoff felt that with advancing age there was tissue phagocytosis and also auto intoxication in the form of toxic absorption of the products of intestinal decomposition both of which Nascher considered untenable

Sir Victor Horsley thought that progressive aging was due to dysfunction of the thyroid gland

Lorand extended this endocrine aspect to inculpate all of the ductless glands Still others sought to demonstrate aging effects as being wholly gonadal in origin

Naunyn attempted to show that the wear and tear of tissues during activity, with inadequate repair (catabolism overshadowing anabolism) associated with an impairment of the heat regulating mechanism could account for senile change

Canstatt, at the time of the exposition of the cell theory in biology, ascribed total body changes to the fact that the death of the cell was so much molecular death of the organism which was not replaced

Nascher elaborated on the theory of cell tissue evolution, assuming that as cells change they are less fitted to adapt themselves to new environments internal or external so that inadequate and nonadaptable cells develop eventually

Bogolomets suggested that the age of the organism is equivalent to the age of its connective tissue The structure and condition of the connective tissue cells determine the organism's resistance to infection and its predisposition to cancer and to senile changes

Duran Reynal s studies indicate that with increasing age there is increased resistance to infection which may modify the process in such a way that its manifestations are unrecognizable as compared to manifestations of the same infectious agent in the younger individual' Possibly many features of older age belong in this category of response

41. GERIATRICS

Causes of Death

THERE are five major agents which terminate life (1) infections (2) metabolic disturbances (3) degenerative diseases, (4) malignancy and (5) accidents or other precipitate causes of death

In 1911 the ten leading causes of death included five infectious diseases three degenerative ailments accidents and cancer (see Table 55) (Nephritis is classified under the degenerative diseases)

TABLE 55 LEADING CAUSES OF DEATH 1911

1 Tuberculosis all forms
2 Diseases of the heart
3 Influenza and pneumonia
4 Chronic nephritis
5 Accidents all forms
6 Cerebral hemorrhage and paralysis without specified cause
7 Cancer all forms
8 Diphtheria
9 Diarrhea and enteritis
10 Typhoid fever

By 1935 there were but three infectious diseases in the first 10 causes of death (appendicitis being classified as an infection) four degenerative ailments cancer, accidents and a metabolic disease and their

TABLE 56 LEADING CAUSES OF DEATH 1935

1 Diseases of the heart
2 Cancer all forms
3 Influenza and pneumonia
4 Chronic nephritis
5 Tuberculosis all forms
6 Cerebral hemorrhage and paralysis without specified cause
7 Accidents all forms
8 Diseases of the coronary arteries and angina pectoris
9 Diabetes mellitus
10 Appendicitis

order in the table had cl see Table 56)

By 1945 the list had ch and numbers There remai tions five degenerative ail accidents and a metabolic Table 57)

These tabulations are unsat several influences may be ope one condition They are howe indicators of the changes in death in one generation *

TABLE 57 LEADING CAUSES OF DE

1 Diseases of the heart
2 Cancer all forms
3 Diseases of the coronary arteries pectoris
4 Cerebral hemorrhage and paralys specified cause
5 Accidents all forms
6 Tuberculosis all forms
7 Chronic nephritis
8 Influenza and pneumonia
9 Diabetes mellitus
10 Cirrhosis of the liver

Tuberculosis as an example of a infectious disease has dropped from place in 1911 to fifth in 1935 and six 1945 Its percentage incidence is re tively 18 5 per cent 7 per cent and 5 2 cent Meanwhile cancer has risen fr seventh to second place in the mortal tables with a rise in percentage incider from 5 4 per cent to 15 6 per cent Th degenerative vascular diseases have gone first place from 24 3 per cent to 53 9 pe cent and progressively increased their lead

* These tables are taken from Louis I Dublin Health Progress New York Metropolitan Life In surance Co 1948

GERIATRIC ANATOMY

The average state of organs in older bodies can be suggested by describing the recurring characteristics in a series of them There is a tendency to a decrease in the size and number of functioning parenchymal units Bulk is maintained by an increase in interstitial volume consisting of pigment blood cells fat and extracellular fluid There is an increase in collagen, a material of lower order There is lessened tissue permeability due to reduction in hyaluronidase or to changes in the hyaluronic acid content of the ground substances or both

Tissue resistance as well as methods of tissue repair are influenced by the several changes as well as by reduced production of enzymes

Changes in the nuclei and nucleoli of cells of several organs have been noted Evidently all parts of the body from the innermost cell structure its protoplasm and semipermeable membrane up to the entire systemic organization are affected by the aging process

The Economy of Aging

Although much remains to be described it may be concluded that the anatomy of geriatrics is characterized by *a pattern of economy* a pattern in which there is an effort to conserve, almost regardless of the nature of the material used in order that the whole organism can maintain a relatively stable and resistant structure to stresses

The physiology of the older body is characterized by an *economy of use* in which energy is conserved as a matter of necessity even though in the conservation important balances may be jeopardized The loss of calcium and protein with prolonged recumbency while not restricted to the aged is an example of effects resulting from this cautious metabolism Minimal rather than maximal reactivity is the physiologic characteristic of higher age—abetted by morphologic limitations In youth there is a carelessness of energy a wealth and enthusiasm with which a seemingly endless reserve of energy is utilized not only for the major functions of the body but also for minor ones The contrast is apparent in the distinctive manner with which an older person and a child cross a room to perform the same deed the one careful, direct and guarded the other carefree careless and casual

Homeostasis

In the need for the maintenance of balance the physiologic inertia of the older body is best understood Homeostasis is synonymous with the preservation of equilibrium or balance Broadly, it is the ability of the older body to walk a tight rope between the changes attendant on aging and the stresses of infection metabolic dysfunction, fatigue and an impaired reactive rate 'The homeostatic mechanisms when subjected to stress are revealed to be more and more limited in their ability to preserve uniformity of the internal environment as life advances into the last decades As long as the body is able to respond to what it must do, as long as there is enough elastic recoil to meet the average and some unusual situations homeostasis is achieved and existence is possible If any stress is exerted sufficiently long to disturb the balance, a series of events may be initiated which can end fatally

Bed Rest and Homeostasis *Failure to follow physiologic principles in therapeutic planning may do the same Insistence on prolonged bed rest is a typical example Associated with the recumbency are reduction in circulating rate and at least temporarily an increased blood volume and increased venous pressure Edema pulmonary and peripheral with expansion of the*

Anatomic and Physiologic Considerations

THE CONCEPT OF HETEROCHRONY

Cells tissues, and organs follow individual life cycles The mind finds it difficult to accept or realize that it resides in an anatomic ferment of cells being born, wearing out dying being regenerated resisting or yielding to disease or that the body is a repository for long dead organs

The short life of a single erythocyte is relatively unimportant the life cycle of the liver is comparatively ponderous and sluggish but vital to survival of the whole organism Between these extremes there are many variations Stieglitz has used the term *heterochrony*, considering the total organism as a constellation in which are many organ satellites Each of these travels its own charted circuit in a multidimensional scheme of physiologic change For example, the orbit of the umbilical cord and of the ductus arteriosus normally come to an end with birth The thymus has a cycle so definite that it could serve as an archetype of body change it develops serves its purpose and having contributed its specific features to the growing body is immolated as a lump of fat and fibrous tissue in its somatic crypt Its function is usually completed but it persists until the body goes through the multiple cycle of all of its parts ending only in the termination of the personality at death Within their own tissue and time cycle the gonads progress in the same manner The intricate series of ascendancies acmes and defervescences can be reviewed without arriving necessarily at a biologic understanding of their causation unless one resorts to an escape into teleology

As complicated as are the uninterrupted natural body changes it is even more confusing to attempt to understand the body reactions to foreign influences which have their own heterochronous behavior Inflammations, infectious diseases, and metabolic limitations implicate organs in interlocking orbits with the rest of the body resulting in interferences identified as specific abnormal clinical processes

"NORMAL" AND "PATHOLOGIC" IN GERIATRIC ANATOMY

To attempt to describe static pictures in this physiologic nebula would be unsatisfactory To do so would be almost as misleading as were the detailed drawings of the nineteenth century histologists, who seemed to be attracted as much by the artistic qualities of their preparations as by the basic structures If descriptive pathology is considered in the sense of the usual fixed and stained standards, then normal geriatric anatomy is synonymous with pathologic anatomy This is a matter of definition If certain deviations from accepted normal are found in most bodies of certain age, then the meaning of normal and pathologic for that age must be redefined

In that sense *average* older anatomy is as much to be expected as are the forms of normality in other stages of life *The new deviations may be expressions of the manifold adjustments necessary to attain higher years* They have been identified as pathologic and therefore bad, rather than as possible beneficial markers in the course of living In making such decisions, it is only by correlating part against function, morphology against its physiologic reactivity, that the proper conclusions be drawn The ultimate aim in the evaluation of standards is to make an estimate of the kinetics of the part and to assay its homeostatic value

quate cellular oxygenation while circulatory resources are under strain to meet more distant demands what extra measures must be utilized to safeguard a kidney just maintaining compensation while an acute systemic battle is being waged?

Fortunately increasing familiarity with the multiple pathologic aspects of the older organism produces a feeling of limited optimism Often a process is remediable which on elective and more restrained consideration would seem rather hopeless The "multiplicity, chronicity, and duplicity" of disorders of the older body have some extenuating qualities, one of which is the possibility of restoration of systemic order despite major body defects

On the pessimistic side are the repeated disclosures of pathologists An older patient may be studied and directed seemingly adequately with a comprehensive view to the diagnostic problems yet at an eventual autopsy one or more wholly unsuspected pathologic conditions are disclosed Although disturbing and a threat to confidence this only emphasizes the peculiarly seclusive nature of the older body However, this older body has the ability to encompass and to some degree, hold in check serious pathologic conditions until the entire mechanism gives way under the accumulated load of unbalanced abnormalities Sometimes only minor disturbances an acute upper respiratory infection, a fall or a new grief are sufficient to tilt the physiologic balance

In conclusion, the determination of the primary diagnosis in geriatrics is essential as in all medicine In the diagnostician's analysis, however, there must be repeated reviews of general constitutional factors until the impending breach of health is mended The dominant ailment always blends into an inseparable pattern against its backdrop of associated pathologic conditions

PERSONAL HISTORY

The eliciting of a complete history from an older individual is not quite the simple task that it is with the average adult Many older patients are unreliable Factors such as memory, fear, deceit, degree of importance, impaired reactions and the skill of the questioner affect the data obtained The physician must recognize that he is dealing with the details of ancient history The older individual, as a rule, confronts his examiner with a group of symptoms with which he has become distracted There may be confusion due to a tendency to hold desperately to one complaint as if fearful that a frank discussion of all elements will be productive of things about *which the patient does not want too much* information

A single symptom may be described with minute detail unless the examiner succeeds in directing the flow of necessary information At the first interview, it may be practical to proceed with symptomatic care to establish *rapport,* realizing that while the physician is evaluating his patient, an evaluation is proceeding at equal pace on the other side of the desk A useful policy is to permit the patient, with some encouragement, to tell his story in his own way, regardless of irrelevancies and sequences At least a start will have been made and it is not unusual at later review to find a number of clinical leads uncovered in this introductory rush of words

A record of this first meeting in detail for potential diagnostic analysis should be kept When this preliminary stage is over it is not difficult to introduce systematized questions If there is a tendency to ramble and to reminisce a pointed question, usually accepted gratefully, may recapture the chain of thought

The jumbled history is not wilful important details may be considered as being too trivial to mention, illness or mental change may cloud memory and contribute

extravascular space follow Aside from changes in electrolyte balance and osmotic pressure caused by protein and calcium loss, carbon dioxide is retained together with water, local tissue resistance is lessened by ischemia, thus setting the stage for infected decubitus Meanwhile, pulmonary stasis is preparing a more dangerous state

Due to this combination of local tissue damage disturbed chemical adjustments, and impaired circulatory dynamics general physiologic integrity is threatened Death may eventuate from sepsis circulatory failure, embolism pneumonia biochemical inadequacy, or combinations of these causes The original condition for which the bed rest had been planned might have been comparatively trivial compared with the chain of circumstances initiated by what was considered to be the proper procedure to cope with it If the emphasis is solely on the primary ailment without regard for the factors governing the older body s homeostasis, the end result can be unfortunate

In older age the ability of cells to multiply normally to grow and to repair damage is modified Whether there is gradual reduction in the rate of tissue oxidation impaired circulation modified immunologic mechanisms or reduction in neuromuscular reactions the ultimate cumulative picture is seen in aging There seems to be a tendency to vagal dominance which may be primary, secondary to lowered sympathicotonic tone, or reflecting increase in levels of body potassium Finally, there is a reduction in compensatory ability in the elasticity with which one system chemical, physiologic or anatomic can offset stresses which in the younger body are checked with greater facility until balance is restored

Procedures in Diagnosis

THERE are as indicated two essential characteristics of the older body (1) an economy of pattern as the morphologic tendency and (2) minimal rather than maximal reactivity as its physiologic norm

MULTIPLE PATHOLOGY

In diagnosis it will be observed that the older body yields its secrets only with reluctance Good clinical judgment is essential to bypass obvious degenerative processes to select which one or which group are responsible for the immediate clinical problem

The older body is a monument a mechanism which has been subjected to metabolic strain, infectious insults traumatic persecution and finally to a number of degenerative limitations The aim of limiting diagnosis to a single etiologic factor for disease has been a valuable concept in medicine It is not easy to change this training to disregard a host of definitive diagnoses and to select the one condition which seems most dangerous to the balance of the impaired functional units for therapeutic effort The status of the patient prior to the acute process must be evaluated because of complementary relationships to the currently destructive condition

How much can an impaired coronary vessel tolerate in the course of a major medical or surgical emergency? Will inactive pulmonary tuberculosis become activated during the course of an acute infectious state or as the result of a therapeutic measure? Will diabetic equilibrium be upset will an old emphysematous congestion stand up to new burdens, can damaged cerebral vessels maintain ade

ment of a degree sufficient to produce focal effects The involvement may be in a silent zone, or may be transitory during a physiologic disturbance In single gross or multiple minor cerebral vascular changes the *act of crying* may occur with or without immediate realization In the vasomotor disturbances of the climacteric and post climacteric states degrees of apprehension occur which can cause crying It also may result from long standing emotional instability or by the failure of the older patient to maintain emotional balance as the declines to age remove the normal restraints of maturity The loss of processes blocking inhibitory controls may be of serious prognostic significance In some people in whom ease of crying was manifest through out life this symptom is of lesser importance than in those in whom such manifestations are unusual In the latter, this single form of expression may justify a complete neurologic examination

Dyspnea* Dyspnea is a stressed respiratory effect which results from one or more factors which increase oxygen requirements or necessitate increased elimination of carbon dioxide It is one of the earliest manifestations of aging and causes the patient to reflect on his beginning physical limitations Generally dyspnea in the older person has organic significance It is of importance diagnostically and from the aspect of promoting comfort to realize that several active causes may be involved simultaneously

The etiology may vary from the ability of blood to take up essential gases to gradual failure of the circulatory pump to make the circuit possible or the lessened ability of the thoracic cage to contribute to the blood flow and the quality of the pulmonary exchange as well as disturbed caliber of the respiratory structure Abnormal chemical states in metabolic disorders reception by the primitive and by the more highly developed respiratory centers, and sensitivity to cerebral stimuli resulting in disturbed breathing must be evaluated

Fatigue Fatigue is so subjective and so indefinite as to warrant a thorough study even if the complaint gives the impression of being psychogenic in origin It cannot be overlooked or accepted with complacency unless adequate evaluations of the older system have been made Infections metabolic disorders secondary to renal impairment or to myasthenia gravis, malignancy, malnutrition, anemias and vascular impairments may produce a sensation of tiredness on lesser effort The diagnostic investigation is conditioned by the longer time necessary for the average older person to recover abilities after effort

Indigestion Indigestion is a vague term having different meanings to different individuals Generally it is a pattern of changed appetite, food fears and a variety of abdominal and referred sensations arousing consciousness of a function that does not usually enter consciousness It can result from disturbances of many body systems and is mentioned to indicate the common error of treating it as if it were always a reflection of gastric hyperacidity Vascular limitations may produce as much digestive disorder as digestive enzymatic inadequacies Functional disorders may equal all organic causes in numbers Nevertheless these belong at the bottom of the list of *preliminary diagnostic impressions*

Depressed States Depressed states are common in the older age group, frequently being present in the early morning and lifting after activity There may be a variety of causes but whether primarily due to emotional or somatic change it is taxing to patient and physician This state may be masked by many physical symptoms making it difficult to establish which is primary The possibility of compulsive and impulsive suicidal tendencies is a periodic danger Every degree of depression must be ap-

* See also Chapter 44

to confabulation, the desire to aid the physician coupled with the desire to be helped painlessly may be associated with evasions to avoid those obvious conclusions necessitating extreme diagnostic or therapeutic measures Information may be withheld through fear and long past, even though important illnesses may have been forgotten in the lethargy of the older body Rheumatic fever, malaria in an earlier day typhoid fever, a spot on the lung' or a penile lesion may have been lost in memory almost completely Previous errors in diagnosis have been sources of misinformation carried over decades Generally, however, with patient effort sufficient background can be established to serve as a useful history

SYMPTOM HISTORY

Certain complaints recur frequently in the geriatric medical story Every clinician s fund of experience contains the symptoms listed in Table 58

TABLE 58 COMMON GERIATRIC SYMPTOMS

1 Anorexia
2 Bad taste in the mouth
3 Constipation
4 Cough
5 Crying spells
6 Dyspnea
7 Fatigue
8 Indigestion
9 Mental depression
10 Nocturia
11 Nocturnal leg cramps
12 Paresthesias
13 Precordial distress
14 Shoulder back and other joint pains
15 Tinnitus
16 Vertigo
17 Visual disturbances

Common Symptoms

Anorexia This may have a variety of origins, organic, psychologic, and social Organically, there may be loss of sense of taste or smell primary disease of the gastro intestinal system or renal disorders In wasting pathologic processes, malignant, infectious or metabolic, loss of appetite can impair other measures of treatment The individual may lack stimulus to eat from within or without Due to monotony, lack of incentive, or obscure emotional reactions, there can be apathy and rejection of the security represented by normal feeding Contrarily, bulimia can occur as a reaction to some of these etiologic factors

Bad Taste in the Mouth This may result from primary oral conditions such as dental or lymphoid sepsis, reactions to dentures, infections, ozena, or be associated with achlorhydria and various gastrointestinal and electrolyte disturbances A depressing and difficult situation occurs if there is intractable involvement of cerebral taste centers

Constipation As a primary state, it is probably not a great deal more common in older years than in younger

Cough Cough is a disquieting symptom at any age, but never more so than in the older individual who too often takes it for granted The increasing incidence of pulmonary malignancy the high frequency of active pulmonary tuberculosis in the aging and the association of cough with important pathologic states should be borne in mind Cough may be an expression of dyspnea hyperventilation habit desire for attention sinobronchial syndrome as well as vagal stimuli pleural irritation, and aural cerumen impactions It should be a rule in geriatric practice that every cough be considered an indication of serious disease unless using every reasonable measure, it can be proved otherwise The integrity of the cough reflex may be reduced by lessened sensitivity or by general weakness The reduction of tussive effectiveness may be the preliminary to a pulmonary complication

Crying Spells Crying spells may occur when the cerebral centers which control emotions have undergone vascular impair

scalenus anticus syndrome sympathetic dystrophic states and local trophic effects may follow the widespread structural changes. *The accentuation* of vertebral curves *cannot* occur independently of the many segmental and coelomic adjustments *that must occur* if skeletal and chemical *balances* are to be preserved

Tinnitus Ringing roaring or hissing in the ears is associated very frequently with vertigo * Certain drugs such as quinine aspirin and others may induce this feeling

Vertigo Vertigo seems to be easily induced in the older individual due to relative inelasticity of the vascular electrolyte systems *There* are many other conditions associated with this unpleasant reaction *often transient* and unimportant but periodically the cause of serious traumatic accidents One of the commonest causes is orthostasis so that many people of this age bracket begin and end every day with a brief wave of vertigo In vascular cerebral states particularly when parenchymal damage has occurred and in cerebellar diseases the sensation of imbalance is common In acid base disturbances and in some cardiac states such as Stokes Adams syndrome particularly in the presence of anemia it may arise periodically with various degrees of intensity

FAMILY HISTORY

The older patient is the incarnation of his family tree He may have lived long enough to manifest or to escape the familial diatheses It may be quite impossible to *get an accurate family history from the patient but inferences regarding general* trends may emerge from the examination For example the tendency to gallstones or hypertension or faulty fat metabolism may be as apparent as is the physical structure or the character of pigment distribution

This phase *of investigation* is *often* by passed although it can be a fruitful source of diagnostic information As a major contribution to geriatric knowledge based on correlation of the individual and his family *history* it would be rewarding Such data is available only in some families

* See also Chapter 56

SPECIAL SYMPTOMS AND SIGNS

Similarities and contrasts in certain *symptoms and signs exist in comparison to younger persons*

Pain

Pain is a perverse symptom in young or old which may guide or mislead the physician Although the sense of pain seems to be the least affected by aging (Stieglitz) dulling of mental reception or perversity of this sensation may modify the nature of the complaint In younger persons inflammatory disturbances of serous surfaces are accompanied by severe distress an older person may not suffer with the same intensity from an identical condition

Acute pleuritis pericarditis and even perforative peritonitis are often relatively painless Cholecystitis cholelithiasis *appendicitis gastric and duodenal lesions* and acute pancreatic necrosis may evoke little or no suffering Coronary thrombosis without pain is not unusual at any age but is more common in senility The extrahepatic biliary passages may be filled with calculi the common bile duct suddenly obstructed a communicating fistula established between gall bladder and transverse colon yet the patient makes no complaints referable to the biliary system renal stones may pass down the ureter into the bladder without provoking colic large ulcerating lesions of *the gastrointestinal* tract are often free of discomfort while carcinoma of the stomach may fail to produce either nausea or other complaints

On the other hand marked distress may accompany diseases of joints muscles nerves and blood vessels (Mueller Deham

proached as a problem in rehabilitation and few conditions are more difficult of solution

Nocturia Nocturia in older age is associated commonly with prostatic enlargement but may be a symptom resulting from a group of changes There may be various modifications of the bladder mucosa or wall urethral irritations and interferences inflammation of urethral glands, and dilated veins in the area of the urethra traversing the prostate Genitourinary malignancy diabetes of both types loss of kidney concentrating ability and compensatory excretion in cardiac decompensation must be considered A neglected hernia, cystocele or urethrocele may influence urinary frequency Habit is a very common cause Nocturnal restlessness due to cerebral anoxia is responsible for getting up to void and the activity increases carbon dioxide elimination by stimulated pulmonary ventilation There is evidence that carbon dioxide retention is associated with water retention and reduction in its concentration is accompanied by water loss Neurologic and disturbed cerebral states often have accompanying changes in habits of micturition

Nocturnal Leg Cramps There are many considerations in determining the significance of this manifestation which may be very mild or so frequent as to disrupt rest One partial concept is that the cramps can be localized areas of tetany in muscles sensitized to local calcium deficiency The symptom may indicate the need for investigation of acid base and electrolyte balances Many measures have been effective, such as quinidine sulfate antihistaminic drugs vitamin D sodium chloride androgens estrogens high protein diet hydrochloric acid increased physical activity and vein supports

Paresthesias Paresthesias are abnormal sensations arising from a variety of causes Chemical imbalances neurologic disease locally or centrally, and local pressure effects can produce the same symptoms of changed sensation

Precordial Distress Precordial distress of any type is ascribed rather automatically to cardiac ischemic states This is a rational approach but it must be recalled that there are many causes for the symptom and that cardiac vascular occlusions can occur without it Many modifications of the thoracic structures may induce precordial pain namely, rheumatoid arthritis of rib articulations, intercostal nerve and muscle conditions such as herpes zoster and trichinosis and referred pain from dorsal root irritations A retrosternal thyroid other mediastinal masses and hiatal herniations must be considered Referred pain from esophageal gastric and duodenal conditions may be felt partially or exclusively as chest pain In severe anemias and so very often in functional states such as neurocirculatory asthenia this may be a common distress Pleuritic and pericardial irritations may be the cause Biliary, pancreatic, diaphragmatic and even renal disturbances may incite chest pain As in all of these symptomatic states accurate determination of the underlying cause is essential not omitting the usual precaution of multiple etiologic contributions

Shoulder, Back and Other Joint Pains These complaints may be due to various forms of arthritis fibrositis and ligamentous changes as primary states or secondary adjustments in the skeletal structure Postural changes with new muscle stresses and strains are associated with replacement of muscle fibers fat and hyalin deposition, or even calcific deposits A discomfort which begins in a local joint area may have its scope extended over a large area by way of the fascial planes muscles and nerves involved One particular site of predilection in the older body is the occipital cervical pectoral zone in which neurologic, muscle, vertebral and other changes occur A

disease Dyspnea is relatively easy to precipitate because the respiratory mechanism is very sensitive to pulmonary insufficiency due to changes in the oxygen and carbon dioxide alveolar and blood concentrations The tendency to a higher body content of carbon dioxide is a reflection of lesser physical activity has a bearing on the general electrolyte reserves water balance, and renal activity as well as the respiratory rate

During the routine inspection of a hospital chart the pediatrician notes temperature changes first and then the figures for pulse and respiratory rate In the clinical record of an older individual the first warning signals are manifested often by a rising respiratory rate Having less reserves for error the first lapse of observation in the older patient may result in the development of irremediable change

Weight

Weight fluctuations in the higher age group are subject to the same precautions There may be progressive loss in weight without particular hazard associated with vascular limitation cerebral changes, or elimination of edema However symptomless loss may be the only prominent indication of a malignancy, an overfunctioning thyroid gland a dull but active pulmonary tuberculosis a low grade renal infection as well as nutritional imbalance Changes in weight up or down may be masked by protein calcium, sodium and water imbalance The gain in weight due to water retention or in myxedema may mask a basic loss A constant check of this physical characteristic may instigate studies in diagnosis without other apparent reason Some geriatric patients seem to go through troublesome cycles of weight loss that are a constant source of diagnostic worry and for which cause is not found This while not uncommon does not permit neglect of a diagnostic survey when weight loss occurs

PHYSICAL EXAMINATION

The older body has been succinctly and thoroughly described and requires no additional generalizations, but the alterations of age change the values employed in physical and laboratory diagnosis

Integument

As a rule there are marked changes in the skin particularly in those parts exposed to sunlight, cold, wind, and to occupational forces, such as blast furnaces and ultraviolet light Habitually covered parts usually remain remarkably supple The typical changes consist of wrinkling loss of elasticity, thinning pigmentation, vascular modifications, changes in hirsutism, and the accumulation of varied lesions from the several skin layers The quick sensitive changes of the younger epidermis have disappeared and it becomes more difficult to distinguish between normal old skin and the pathologic form The flush of fever, the prominence of jaundice, the bold pigmentation patterns of certain diseases may not be so apparent Functions such as transfer of water, excretion, lubrication, and heat control, while maintained fairly well in unstressed states may not prove adequate in preserving homeostasis during emergencies

The deposits of fat around the skull often are reduced so that enophthalmos prominence of ears accentuation of the nose and facial contour are changed The eyelids share the skin changes and the cilia lose their orderly direction The lower lid frequently is thickened with edema An atrophic nasal mucosa and thickened ear drums may be found in addition to many other modifications in these two organs

Mouth

The gentle droop of one lip may be an indication of Parkinson s disease or a memento of a cerebrovascular accident Lip color and texture may give the initial lead

and Rabson) Pain as a diagnostic aid is possibly less reliable and may not be elicited as often in older patients This emphasizes the need for fine distinctions in the investigation of any distress

Complaints of mild pain in certain locations and of a certain character, when associated with suggestive features such as jaundice, hematuria dyspnea, or distention, should stimulate the same degree of medical or surgical urgency as will acute suffering Diagnostic acuity must be made an adequate substitute for the modified pain warnings of the old body

Fever

The degree of fever in any state of debility—in extreme disease or extreme age—may be impaired The character of the response, typical or atypical, is bound up with a host of factors such as antibody reserves chemotactic qualities hyaluronidase titers, globulin modifications, and steroid production Although older patients can and frequently do manifest excellent temperature reactions labile manifestations such as psychogenic hyperthermia are less common, and the temperature level like the cardiac rate tends to approximate a fixed and limited range

Failure to note and to explain the reason for relatively minor elevations of temperature in the elderly may be responsible for the difference between accurate and inaccurate diagnosis Frequently at autopsy unsuspected pulmonary disease pyelonephritis, thrombophlebitis myocardial infarction or other conditions often associated with fever have been demonstrated A review of the clinical chart may have shown only minor variations in daily temperature recordings

In general any elevation in temperature in older individuals which is persistent even though not associated with symptoms should precipitate investigation until an explanation is obtained It should be a rule to investigate at least for the following infarction, possibly but not necessarily myocardial, pulmonary consolidation, pyuria, phlebitis and diverticulitis This list omits a host of possibilities, such as malignancy, including lymphoma, as well as those fevers associated with involvement of the cerebral parenchyma, but by following it a number of unexpected lesions may be found at a stage when they are more manageable

Pulse Rate

The pulse has a tendency to be lower, possibly indicating additional evidence of the increased vagal tone of the older body Disturbances of rhythm, such as auricular or ventricular premature contractions and auricular fibrillation, are not uncommon Sinus arrhythmia, however, is less usual In advanced old age the rate usually becomes accelerated A persistent, rapid rate even though not associated with striking additional manifestations may be the only indication that the body is straining to maintain normality in the face of beginning myocardial impairment Tachycardia may be an indication of anoxia due to respiratory encroachment denote progressive anemia or a hypermetabolic status (such as hyperthyroidism) masked by an old frame

Since there is a tendency toward an inelastic fixation of pulse rate, the onset of an unusual rate or rhythm must prompt active investigation Failure to heed changes at a time when treatment may be relatively easy and effective can permit the development of severe disorders.

Respiratory Rate

The respiratory rate does not vary from that in average maturity, being 12 22 per minute, but this too is less subject to superficial variation than in younger years A rising rate may be significant of serious

roentgenogram There is a deepening of the hilar shadows, general increase in the various pulmonary markings, fair diaphragmatic excursion, and a tendency for separation of the heart shadow from the anterior chest wall due to the increased thoracic anterior posterior diameter

Inside the thorax of the older patient the carina of the trachea has a new landmark below the level of the sixth dorsal vertebra The cartilaginous rings of the trachea and bronchi tend to fibrose and calcify, as do the cricoid and thyroid cartilages The mucosal lining of the respiratory tract is thinner, and functional continuity is impaired because of loss of secretory and ciliary cells These increasing limitations are in contrast to the proliferation of functioning epithelial units in islands of hyperplasia The lung parenchyma site of dust pigment and other depositions, has thinner alveolar walls with obliteration of some septal capillaries, a decrease in the number of air cells due to fusion of groups of them increased fibrosis, and a total decrease in weight of 25 per cent.

A line of dilated or broken venules may be seen on the chest surface marking the diaphragmatic attachment, and if excessive, are suggestive of decreased capillary resistance to trauma Prominence of superficial veins suggests interference with blood flow into the vena cava and the establishment of collateral channels The sternomanubrial angle becomes thicker and more prominent as the sternal bones fuse The axillary spaces seem deeper due to loss of fat deposits Clavicles and scapulas may stand out with the fat loss and changes in muscle bulk The mammary areolas often are darker Systolic and inspiratory retraction of intercostal spaces are seen more commonly than in younger persons

Palpation On palpation, various skin modifications are noted quite commonly, such as lipomas sebaceous cysts telectangasiae, keratoses pedunculated verrucae, and enlarged lymph nodes The latter may be indicative of underlying infection or a form of malignancy Apical cardiac impulse may be somewhat obscured by overlying lung or by the fact that it is not quite transmitted to the chest wall, particularly in the recumbent position The perception of thrills may be obscured in the same way Delineation of cardiac borders by percussion is less accurate Hyperresonance is the more typical percussion note Since the more rigid wall resonates as an entity, transmission of the percussive force is diffused more widely and tends to obscure lesser areas of intrathoracic change Due to pleural changes, formation of blebs and other pulmonary modifications the value of percussion as a procedure is impaired Major anatomic changes may occur before they can be detected by this single physical method

Auscultation By auscultation the heart sounds may be somewhat distant, lessening the ability to evaluate valve or muscle tones but generally this procedure is quite adequate Physical changes can be compensated by postural manipulation of the patient, and by regulating the respiratory cycle when possible

The characteristic bronchovesicular sounds may obscure lesser noises and overshadow fine râles A rigid bronchus fixed to fibrotic dense tissue and thickened pleura may have an amphoric quality simulating that heard over an open cavity

Abdomen

The structure of the older abdomen is modified by the accentuation of the vertebral curves With loss of tone of the stomach wall musculature, the normal and abnormal contents of the coelomic cavity are felt more readily On inspection with the patient recumbent the curve of the fixed horizontal costal margin stands out with its fixed and often prominent xiphoid process as a tiny keystone in a large arch

to circulatory failure and other conditions Changes secondary to variation in abutment of lip edges may be the result of dental or denture defects, untended nocturnal salivary drooling, local infections, or a part of the picture of ariboflavinosis Blood dyscrasias nutritional imbalances, calcium loss and local as well as constitutional infections may influence the state of the dental ridge and its structures The tongue may be suggestive of changes in the gastric mucosa It may be thinned, smoothened with papillary atrophy or reddened in deficiencies associated with certain diseases Muscle changes in neurologic states, tremor state of hydration and sublingual varicosities are of diagnostic significance

The ratio of secretion of salivary mucus to serous material as well as the secretion of specific chemicals like ascorbic acid by the salivary glands participate in the aging changes In general there are few abnormal processes which are not reflected in some manner in the oral cavity

Neck

Examination of the neck reveals enlargement and increased firm texture of the submaxillary glands, possibly paralleling similar changes in gland complexes elsewhere in the body The central neck structures anteriorly are usually more prominent and less mobile than in younger persons Loss of fat depots thickening and tortuosity of blood vessels, changes in vertebral structures and curves, and rigidity of muscle planes, modify the neck contour

With the sternum being higher, there is a lessening of the mental suprasternal distance making thyroid modifications harder to detect To accommodate to these changes, the posterior neck muscles become larger and firmer, with the development of a series of changes frequently responsible for brachial plexus or posterior occipital nerve symptoms

Changes in the cervical vertebral relationships account for many vague and distressing symptoms referable to the back of the head the neck, and involving the entire pectoral structures The normal cervical arch is modified in relation to the other vertebral curves and accompanied by pelvic and femoral realignment, so that the head often is carried forward and down Changes in vertebral ligaments intervertebral cartilages, and the bones themselves result in new stress lines and a less stable posture Many soft tissue adjustments must be made to accommodate to the changed musculoskeletal structure The fibrositic, arthritic, and nerve root pains localized in the neck or extending to scalp and back are unpleasant accompaniments of the changes in aging skeletal balances

Thorax

Examination of the thorax proceeds properly from that of the neck since any radical change in the latter s landmarks may imply major intrathoracic causes However, the older cervical structures are less mobile and may fail to shift as much as in younger bodies in adjustment to massive pleural effusion large areas of atelectasis, or extensive pneumothorax The tendency to fixation emphasizes the value of the sign when it is present

The older chest progressively changes toward a state of relative fixation The bones of the sternum tend to fuse together, often with a prominence of the ossified and fixed xiphoid process the dorsal curves become accentuated due to thinning of intervertebral discs, and these two less mobile uprights are joined by ribs which are rotated toward a more horizontal plane in a position of relatively permanent inspiration The costochondral segments tend to become ossified although this change may occur in early years The result is a chest which is deeper rounder, more tympanitic, and less elastic

These bone changes are apparent in the

smooth, dry, and glazed, in many respects similar to the lining mucosa of the older nasal passages Fibroatrophic changes of the uterus, tubes, and ovaries are typical The cervix may protrude quite far down into the vaginal vault due to reduction in tone of the supporting structures The changes in the labial and vaginal linings may proceed to stages of atrophic vaginitis, kraurosis, or leukoplakia These membranes are susceptible to trauma and infection If indicated, cervical smears for differential stains saline washings, and a catheterized urine specimen can be obtained The cervix should be inspected routinely and suspicious areas biopsied

Anus and Rectum The *tone* of the anal external sphincter may be poor, or the orifice can be impaired by scar tissue of local disease or previous traumatic procedures More than half the neoplasms of this part of the colon are palpable, making local examination mandatory The fecal residue on the glove can be checked immediately for occult blood Where there is the least indication, instrument examination should be done, aided by roentgenology

Extremities

In the extremities age changes are early and tend to be extreme Nails are thickened, ridged linearly slow growing and have a tendency to be brittle and to have paronychial accumulations Joints are thickened and may be nodular because of localized accumulation of calcium or the multiple changes of arthritis Thenar and palmar fat deposits tend to be reduced with reduction in interosseal muscle tone and bulk Tendons are less elastic Radial vessels are thickened, may be beaded, tortuous, and rigid enough to move overlying tissues with the thrust of their pulsation Veins are more prominent because of loss of fat sheaths and have reduced accessory pumping aid by less active supporting muscles They may be thickened, tortuous, and the site of sclerotic patches Varicosities, arch changes, and the angle of the feet in walking are end results of skeletal adjustments

Gait

Epicritic senses are more diminished than is deep perception, with a general loss in fine sensory ability Proprioception and vibratory sense tend to be diminished while general reflexes may become hypoactive Gait is modified by neurologic impairment central or peripheral, or reflects the skeletal adjustments to maintain a balanced erect posture It may be manifested by the typical *marche a petits pas* Another modification is knee bending with slight festination to compensate for the general changes in the skeletal superstructure Tremors varying from fine to coarse and involving large areas or only part of a digit are common In some individuals an erect posture, neurologic integrity, and general body tone are maintained to a surprisingly efficient degree and different from youth only in the spontaneity of body action

LABORATORY FINDINGS

Laboratory standards generally have not been tabulated with adequate allowance for clinical individuality for normal older persons These definitive observations are necessary for accuracy in diagnostic summation The recent tendency in studies has been to include evaluations for comparative decades Levels assayed at rest can be inadequate it may take a state of increased stress to expose true differences in physical reserves

Blood

There is general agreement that the average *red cell count* in older persons tends to be lower In one series *two-thirds* of the subjects had an erythrocyte count between three and four million, and the remaining one third was in a range of four

In the upper half of the abdomen the muscles fall away from this vault while in the lower half there is greater bulk due to the drag of relaxed muscles and their greater fat depots

Running the examining fingers down the midline of the abdomen with the patient's head raised from the table may demonstrate certain defects of the wall Generally palpation discloses a reduced tendency to muscle spasm due to a reduction in general sensitivity and reactivity Umbilical diastasis seems to be common and it has been pointed out as a possible sign of reduced thyroid activity Dimpling of operative scars or retraction when lifted, suggest adhesions In the systematic examination familiarity with certain landmarks such as the xiphoid, the pulsating firm abdominal section of the aorta the anterior curve of the vertebral column and a filled colon should allay suspicion of abnormality

The inexperienced may be misled by the ease with which the several structures are felt through the atonic wall To note the edge of the liver below the costal margin is not sufficient to indicate enlargement if the height of the dome has not been determined The abdominal wall and various supporting structures no longer may be capable of giving the customary amount of fixation If the mobile liver falls back into the abdomen with the patient recumbent it can be felt easier when the patient is erect or bent over slightly Anatomic variation as well as the reduction in size of the spleen with age make this examination more difficult The factors of ptosis position and processes that produce chronic enlargement must be evaluated Ability to palpate the gallbladder, pancreas, and left lobe of the liver is an indication of a pathologic condition Tenderness or enlargement of the kidneys as well as their motion on respiratory excursion are judged in the light of increased motility and possible reduction of perirenal fat

Examination of the abdomen by palpation must not be perfunctory It is particularly rewarding in diagnosis in this age group Percussion and auscultation can be important differentiating aids, as in percussing the area of subdiaphragmatic tympany on the right lower costal zone or hearing peristaltic noises over the precordium

Pubic Region

Male Genitalia In the male, preputial and meatal adhesions can be present with little impairment of function An occasional individual will tolerate extreme degrees of urethral obstruction without complaint Due to skin and muscle changes, the scrotum may be atonic and is often the site of a varicocele or hydrocele Comedones sebaceous cysts, and pigmentation changes as well as other common dermatologic variants are to be seen

The average older *prostate* varies too much in size shape and consistency to permit of generalization The size texture, symmetry nodularity calcification response to pressure, and character of the expressed content must be noted Its examination by rectum is an inadequate procedure so that suspicious clinical manifestations must be followed by instrumental chemical and cytologic investigations In the third decade this gland has an average weight of 15 Gm is 25 per cent heavier by the sixth decade and can approach 40 Gm normally by the eighth decade of life General glandular atrophy may occur instead of benign enlargement or malignant change

Female Genitalia* In the female, reduction in fat deposits and associated atrophic changes modify the texture and appearance of the perineal structures The vaginal mucosa tends to become thin

* See also Chapters 28 and 35

gested that *postclimacteric* differences in the level of *uric acid* between male and female were lessened At least the clinical observation of a rising incidence of gout in the menopausal woman is suggestive When young people were compared with an older group uric acid values in males averaged 5 05 *mg per 100 cc*, being 5 0 mg per 100 cc in older males, and 5 1 mg in younger In the females the over all average was 3 75 mg per cc, being 4 0 mg in the older and 3 5 mg in the younger group Blood uric acid was lower in women than in men in all age groups and the greatest difference was *between young and old* females

Total blood *protein levels* are slightly *lower in both sexes in the* higher age groups, the change being due primarily to a lowered albumin level Some compensation is afforded by a rising globulin fraction but this is not sufficient to maintain the average levels of younger years

There was no general pattern of modification *with increasing years in the plasma* levels of nine *amino acids* The average concentration for five of them—leucine, *isoleucine, valine tryptophane, and lysine* —fell with age The average level of histidine rose Threonine, tyrosine, and glycine were not altered significantly

No significant difference is found in *antibody response* in aging using typhoid vaccine

With increasing age, there is a significant reduction in the *p*H of the serum, being 7 37 compared *with an average* in younger years of 7 4 Neither total *carbon dioxide content* of the blood nor *serum bicarbonate are reduced* This measure of acid base equilibrium is considered within limits of normal at rest It is generally agreed, however, that the various components of electrolyte balance are more *easily disturbed* by stress in the older body than in the younger Renal and pulmonary compensating *mechanisms* are less effective in a measured period of time

Some general observations about in organic blood elements are available The amount of *iron* in the body tends to increase with age The *magnesium* level tends to decrease *Potassium* seems to increase but in no consistent pattern

Vitamin determinations in an ambulatory group, on normal diet, aged 65 to 86 years disclosed *the values shown in* Table 59 with no significant sex differences

The mean *plasma tocopherol level* for a 16–59 year combined sex group was 0 90 mg per 100 cc. In the 60–101 year combined group the mean level was 0 99 The mean *male level* rose from 0 83 under 60 years of age to 1 00 over 60 the mean female level rose from 0 955 under 60 to 1 01 mg per 100 cc above 60 years of age

Gastrointestinal Findings

Quantitative evaluations of gastrointestinal secretory components have been made

TABLE 59 VITAMIN LEVELS IN OLDER PATIENTS

Vitamins	*Normal level in blood or urine*	*Av for test group*	*Percentage in group below normal*
Carotene	>100 γ per 100 cc	86 γ per 100 c c	57
Vitamin A	>20 γ per 100 cc	22 γ per 100 c c	43
Thiamine chloride	>100 γ per day	94 γ per day	68
Riboflavin	>0 3 mg per day	0 8 mg per day	2 5
Nicotinic acid	>3 mg per day	9 4 mg per day	0
Ascorbic acid	>0 65 mg per 100 cc	0 88 mg per 100 c c	54
Citation			

From Rajsky and Newman

to four and one half million A study of the red cell count taken under basal conditions averaged 4 65 millions per cu mm for both sexes There is a tendency for the lower count in the female to level off in the higher years The reduced ability to regenerate after acute or chronic blood loss or after marrow depression is a better indicator of hematopoietic reserves than resting determinations

The basal older *hemoglobin concentration* in males ranges between 12 9 and 14 09 Gm per 100 cc, and in females between 9 6 and 13 47 Gm per 100 cc There is a tendency to postclimacteric equalization

Various authorities report the *packed red cell volume* average between 41 2 and 43 69 per cent for males and between 36 7 and 40 46 per cent for females Corpuscular constants, reticulocyte percentages and red cell morphology under basal conditions have been found to be within normal limits although there is a slight tendency in both sexes for the average corpuscular volume to increase with age The mean corpuscular volume has been reported as 88 9 cu $\mu \pm$ 0 70 A tendency to variations in size shape and staining characteristics of red cells may occur in higher years but related factors such as anoxia protein balance and maturation must be evaluated before these changes can be validated

Red cell diameter is reported as averaging 7 5 μ with a range of 6 8–8 μ Mean corpuscular diameter is significantly greater in the aged due to increased quantity of CO_2 in the blood (Olbrich)

The *platelet count* unstained shows no characteristic changes with aging However Sunderman and Boerner state that after sixty years of age the number of platelets is usually significantly lower than in younger persons' Red cell fragility has been reported as increasing with age

There is general agreement that the average *resting leukocyte count* and characteristics are not modified with increased years

The ability of the older body to respond to demand for red blood cells or leukocytes has been reported as adequate but modified in that the time required to return to average levels is longer and the stimulus necessary to produce a response must be greater as well as applied over a greater period of time It is possible that the rate of normal cell destruction is reduced so that more older cells may be present in the circulating blood

As to the *sedimentation rate,* a recent conclusion is that data for the sedimentation rate are so meager that no generalizations can be made

In the measurement of various substances in the circulating blood the basal resting levels generally are not much changed from middle maturity through the higher years Such determinations show the end results of physiologic effort without reflecting necessarily the means by which the body attained those goals Fasting *blood sugar levels* for example are unchanged in both median and range values with the progression of life The curve of *glucose tolerance* has been reported as reaching higher figures and taking more time to return to a base line The delayed return and mild diabetic curves and the continual diminution of normal curves suggest a progressive lowering of the glucose tolerance during the process of aging (Kountz) Average figures reported were 92 9 mg per 100 cc fasting, a level of 132 1 mg in one half hour, and 173 3 mg in one hour None of these patients had diuresis after the glucose was given (Deren)

Fasting *serum calcium* and *phosphorus,* levels show no major differences from younger persons There is a gradual but significant increase in serum alkaline phosphatase activity in both sexes between the seventh and ninth decades

As far back as Hippocrates, it was sug

TABLE 60 17 KETOSTEROID CONCENTRATION

Age	Male (mg /100 cc)		Female (mg /100 cc)	
	Range	Average	Range	Average
18 to 59	6 6 to 18 7	12 17	4 1 to 11 5	5 58
60 to 89	6 1 to 16 5	9 50	4 to 8 7	5 60

From Taylor Brozek and Keys

the urine depends on testicular and adrenal sources in the male, adrenal and ovarian sources in the female Difference in the sexes as to production and excretion tends to lessen with increasing years Table 60 shows the range of one reported series

In another series twenty four-hour neu tral 17 ketosteroid urine excretion was 15 mg in 30 year-old males and 4 mg in older males In females the comparative figures were 10 mg and 2 mg

Androgenic hormone is synthesized in testes and adrenal cortex The twenty four-hour urine excretion in 30-year old males is 55 International Units falling to 8 I U in the 80 year-old male In the female, there is generally only one third of this amount elaborated at all ages, with a pos sible decline after 50 years

Estrogenic urinary excretion in twenty four hours was shown to be 12 Rat Units in young and old males In young females, 38 R U are excreted as compared with 7 R U for higher years

There is a general decline from middle age onward in the urinary *gonadotropins* if one disregards the high immediate post menopausal figures Urinary *11-oxycorti coids* are usually within the normal range Corticoid production after administration of corticotropin (ACTH) is well maintained into the high years, but the response to epinephrine is less sharp

A reduction in *serum acid phosphatase* of prostatic secretions is found with aging Average concentration in young males is 14 400 units per cc In the 16–59 year group there are 11500 units per cc In the group aged 60 to 101, average concentration fell to 5300 units per cc

Serum Iodine

The protein bound iodine of the blood normally is 3 5 to 7 0 μg per 100 cc Values less than 3 0 μg per 100 cc are considered hypothyroid In a series of pa tients aged 25 to 59 the mean serum iodine value was 5 4 μg per 100 cc in the males and 4 7 μg in the females In the same age group, 60–100 years the male serum iodine value fell to 4 0 μg per 100 cc, while in the females the level was 4 4 There is there fore a reduction in this element with age in males, but not in females In this same group of 141 subjects aged 25–100 years the basal metabolic determinations showed a progressive decline in oxygen consump tion with age in both sexes

Metabolic Rate

It was found that with the beginning of general body degeneration there is a lessen ing of metabolic rate in 70 5 per cent of subjects to a level lower than − 10 As the deteriorations progress into the sphere of pathologic limitations only 32 per cent of subjects had a rate less than −10 When there were signs of severe cumulative physi cal impairments with aging only 10 per cent were in the low bracket Apparently the rise in basal metabolic rate is of "bad prognostic significance" in older age "and appears to be evidence of falling reserve (Kountz)

It has been shown that average *salivary ptyalin* concentration falls There is an associated change in the *salivary specific gravity* from 1 004 in youth to 1 009 with age due to an increase of the mucous portion or reduction in the serous portion or both After stimulation in the younger body, the salivary glands produce an average of 14 2 cc. of saliva as compared to the effect of identical stimulation of the older glands which produce an average of 5 8 cc of saliva

With rising age, there is a linear increase in the number of individuals with *hypochlorhydria* and *achlorhydria* The average incidence of achlorhydria below age 20 is at least 5 per cent In the patients above 60 more than one third are achlorhydric the majority of these failing to respond to histamine stimulation

A mean free *gastric acid* content of 47 units was reported in males under 40 with a standard deviation of ± 17 units This value fell to a mean of 33 units in the eighth decade with the same standard deviation Female levels were practically unchanged being 33 units with a standard deviation of ± 15 The number of total gastric acid units for males fell from a mean of 63 5 at 20 years to 55 5 at 60 and 50 5 for the 70–79 group There was no similar fall in the female the figure being almost consistently 50 units (standard deviation ± 15) Male gastric juice volume fell from a mean of 118 cc to 91 0 cc and in the females from 100 5 to 79 0 cc for the same age groups The true achlorhydria in the males below 50 years was 5 per cent rising to 20 per cent for the high ages In the females these figures were 8 5 and 22 6 per cent respectively

Gastric pepsin is fairly well maintained to 60 years of age and drops sharply in the next decade to a permanent low level

Trypsin in the duodenal secretion is maintained until 40 years of age after which there is a gradual drop for the next 20 years to a level which then remains quite constant Upon stimulation, the pancreas can produce the same amount of this enzyme in the higher decades as in the younger

Pancreatic lipase is lower both in the fasting and in the stimulated states

Plasma amylase levels apparently are not affected by increasing years the normal range being 15–35 Somogyi units per 100 cc of serum

Using four standard *liver function* tests in 42 older individuals aged 65 to 86 and felt to be normal clinically, impairment was demonstrated in all but 1 Two of the tested subjects had one abnormal test, 11 had two 22 had three and 6 or 14 per cent of the group failed to show a normal figure for all four tests

Urine

In a group of 36 patients, 15, or more than 40 per cent, had *albumin* in the urine and 9 or 25 per cent showed various types of *casts* The entire group had *urinary leukocytes* varying from few to many Fasting blood *urea nitrogen* and *nonprotein nitrogen* levels were normal The mean blood urea nitrogen content of a large series of individuals over 65 years of age was 36 9 mg per 100 cc with a range of 15 to 58 In this same group the mean urine *specific gravity* was 1 016 with a range of 1 005 to 1 030 Neither of these two evaluations changed to any degree with age Standard *urea clearance* tests and *phenolsulfonphthalein excretion* in 10 older subjects were found to be normal

With increasing age, there is a reduction of 40 per cent in *inulin clearance* by the glomeruli The ability to clear "diodrast" by the tubules is reduced 55 per cent Tubular function suffers greater impairment with age than does glomerular function, as measured by these clearances (shock)

The concentration of *17 ketosteroids* in

average of 43 4, with a positive correlation between the amount of intellectual deteri oration and age Deterioration quotients considered pathologic were noted in 84 per cent, and these did not correlate necessarily with the physical picture The evaluation of the Rorschach test showed correlation with aging as follows delayed responses, reduced number of responses, stereotyped thinking, intellectual and emotional con striction, and impotence in imagination

Summary

The foregoing attempt to summarize some laboratory normals for the older age group must be considered as a *tentative* rather than as a final set of results Many factors require re evaluation, many age dif ferences are not decade multiples which may be reflected in fixed standards many variables enter into the conclusions so that only a wide band of ranges can be *projected* to indicate the trends of older age

Treatment

THERAPEUTIC principles may be de rived from the accumulated data of the patterns of geriatrics The present empiric use of drugs and arbitrary selection of dos ages based on clinical impressions and un critical opinion will be eliminated by broadening comparative pharmacologic investigations to include older groups Therapeutic indiscretions in younger bodies may be buffered by physical elas ticity but are less well tolerated in an older body sustaining equilibrium with more conscious effort

PHYSIOLOGIC AND PHARMACO-LOGIC CONSIDERATIONS

Inasmuch as gastrointestinal absorption is fairly well maintained there is no general restriction to oral therapy Absorption and utilization have a tendency to be slower, so that quicker effects require either parenteral application larger doses, or changes in the rate of administration

Since there is a reduced rate of metab olism drugs will be utilized more slowly and cumulative effects may occur Thera peutic agents whose accumulation can pro duce toxicity must be used more carefully

The general tendency of the older body is to resist change, therefore, when an effect is desired, stimulation is essential The organism may have to be forced with vigor to do what is essential to overcome a pathologic process Contrary to this principle is the fact that where *sedation* is desired, smaller doses should be used

Preparations which contribute to *anoxia* are hazardous because of the tendency to lessened reserve of the cardiorespiratory systems in the older body

Alkalosis has been reported as being more easily induced The electrolyte balance is more readily upset in the aging organism Compensatory mechanisms for control of acid base balance in the lungs, blood, kid neys, skin and bowels are less efficient Use of parenteral fluids must be adjusted to the older patient s needs in time for adminis tration, quantity, and nature of electrolyte composition Chemical determination of key plasma electrolytes should be made to avoid disorders whose clinical manifesta tions may be preceded by blood changes

Drugs having potential *toxic effects* and which are slowly excreted or which are known to disturb electrolyte balances should be given at longer intervals or in smaller doses with constant check of their excretion if possible Occasionally pointed clinical observations may be just as effec

TABLE 61 CARDIAC OUTPUT

Subjects	*Cardiac output* (Cu L./minute)	*Cardiac index* (L./square meter body surf
Young men	5.92	3.08
Middle-aged men	4.66	2.43

From Taylor Brozek and Keys.

Heart

In more than one half of older individuals, the pulse rate approximates 60 per minute with a tendency to higher figures as the very high ages are reached. A tendency to a fixed rhythm is seen in over 60 per cent. The pulse rate in the older age group is less affected by emotional stimuli than in young or middle aged subjects.

Average blood pressures have been cited as being 140/90, a figure meaning little.

The speed of pulse propagation is increased from 6 meters per second at 20 years of age to 8 meters at 60, reaching almost 10 meters by age 80. Circulation rate tends to be slower.

The index of cardiac output declines 1.5 per cent per decade, beginning at age 40. Cardiac output for comparative age groups is shown in Table 61.

Electrocardiogram. There is no absolutely characteristic pattern of electrical potential for the older heart reflected by the electrocardiogram but certain features occur many times more than in younger persons. The tracing must be evaluated in light of the clinical findings. In a large series almost one half had a normal tracing while other series varied from 26 to 85 per cent normal tracings depending on the selection of cases and evaluation of the tracings as well as the standards of judgment. Derived from these investigations are some generalizations which may be more conclusive than the individual findings.

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sedatives The supply should not be available too readily Occasionally the semi sedated older person in his restlessness will continue taking additional doses in a deepening fog of consciousness without memory of prior doses of sedative

ALCOHOL

Unlike sedatives, alcohol is a relaxant in normal amounts, and a toxic depressant in large quantities It does not have excessive vasodepressant qualities Since it decreases anoxia, it may encourage sleep by vasoconstriction of splanchnic and muscle blood vessels and dilatation of cerebral and cutaneous vessels In this manner, the brain is afforded a measure of aid in circulation Many properties ascribed to alcohol are really the results of its transitory sedative effect It has caloric and gustatory values Intravenous use combined with proper electrolytes protein hydrolysates and vitamins can be an important dietary aid for the agitated and debilitated older individual requiring relaxation and quickly available caloric intake

SALICYLATES

These are probably the most commonly used drugs in older individuals and they have a wide range of usefulness Salicylate toxicity generally is low although there are many coal tar sensitive individuals The effects on blood prothrombin, vascular fragility, and reduction in body ascorbic acid stores are quite well known In large doses in sensitive individuals, they may produce a sensation of cerebral fullness with vertigo and tinnitus The depressive and vasodilating qualities have made them serve as mild satisfactory sedatives Older age tolerance is quite high Occasionally purpuric or asthmatic states can be associated with even rather small dosage Antipyretic analgesic, vasodilating sedating general values added to specific use, as in gout, indicate the effective range of application

IODIDES

With exceptions, empiric prescription of iodides has been dominant Including vitamins and hormones, probably no drugs have been used with more frequency for many of the pathologic states present in the higher years It is likely that tracer studies and therapeutic application of radioactive iodine will increase the rational use of iodides Values as lipotrophic agents and in reducing blood viscosity are being investigated Preliminary studies of effects in atheromatous lesions have not been encouraging Early reports of radioactive iodine in angina pectoris suggest benefit under rigid control The entire picture of the management of hyperthyroidism and malignant thyroid metastases has been changed with the development of I^{131} * The use of iodides as a liquefying agent in bronchial asthma is of primary importance

HEMATOPOIETIC AGENTS†

Older individuals tolerate various oral forms of iron despite occasional gastrointestinal distress Depression of gastric secretions may reduce absorption but enough is taken up generally to make this route preferable to parenteral use in all but extreme states of nutritional and secondary anemias Singly and in combinations, liver extract, vitamin B_{12} folic acid ascorbic acid, and iron have been tolerated specific and nonspecific use both being very common Unwarranted or empiric premature use may serve to obscure a developing hematologic pattern prior to the establishment of a definite syndrome Overburdening the reticuloendothelial system may promote hemosiderosis Correc

* See also Chapter 29
† See also Chapter 14

tive—for example, the recognition of low salt syndrome with its characteristic pattern

Certain agents which have potential deleterious effects on systems other than that for which they are being used must be administered sparingly Substitutes in which the side effects have been reduced would be better even if the primary effect desired is not quite as sharp The possible induction of glaucoma by atropine is an example

ADRENERGIC AGENTS

Drugs which stimulate the sympathetic nervous system—the adrenergic agents such as epinephrine, ephedrine, or amphetamine sulfate—are usually given with caution to patients with hypertension and impaired vascular states In view of the general reduced sympathetic tone, possibly increased vagal reactivity, or even general inertia of the older patient, it is to be questioned whether such severe restrictions are necessary Patients with hypertension and asthma seem to tolerate average doses of these bronchodilating drugs with few vascular aftermaths Possibly the coronary dilating properties of such substances—balanced by lesser sympathetic tone peripherally—help to offset the increased effect on cardiac output Empirically, at least their general use seems to increase the sense of well being and in the average older person signs of sympathetic overstimulation are not a common result

CHOLINERGIC AGENTS

On the other hand, the cholinergic drugs are less well tolerated Such materials as morphine, digitalis, and quinidine, all of which have potential extensive use in older individuals, not infrequently produce side effects, or cumulative effects with general evidences of reduced tolerance The infrequent reaction to sympathetic drugs compared with the frequent reaction to parasympathetic drugs is indicative of the physiologic characteristics of the older body

SEDATIVES

Inasmuch as circulatory impairment with anoxia is a constant hazard in the older patient, any class of drugs that might encourage such a state must be used cautiously This is true regardless of the organ which may be involved by anoxia, whether the brain, the heart, the intestines, or other The reduction of the lability of cerebral vasculature and in the rate of drug elimination, together with changes in cellular permeability require careful regulation of sedatives The barbital preparations may give rise to the motor agitation of anoxic states rather than produce the expected relaxation Cumulative effects, nocturnal restlessness, vertigo, memory defects, and other indications of compromise of cerebral compensation may result

Other classes of sedatives such as bromides must be considered from the aspect of tolerance, toxicity, and effects on electrolyte balance The disturbed agitative state of bromism may be confused with cerebral disturbances The possibility of bromide intoxication must not be forgotten In every diagnosis of disturbed states ascribed to arteriosclerosis of cerebral vessels the effects of sedatives must be considered

These limitations must not be too negative Sedative drugs in older persons are important, necessary, and very useful under careful regulation In using them doses should be smaller, and spaced properly They may be combined with caffeine to neutralize cerebral anoxic effects In restlessness due to this type of anoxia, caffeine alone may serve as an adequate sedative Nocturnal restlessness may be due to decreased metabolic activity, the effects of which must be overcome to prevent the inhibition of sleep

Another precaution is that the family should take extreme care in the storage of

habit must always stimulate an energetic investigation Bland nonabsorbable bulk is less disturbing than most classes of laxatives In the act of swallowing the gel like substances precautions should be taken to avoid acute esophageal impaction Older persons can be retrained in proper stool habits and thus avoid the sequelae of persistent laxation These are disturbances in enzyme elaboration water balance, changes in mineral metabolism reduction in reserves of oil soluble vitamins in some instances and interference with several normal colon synthesizing activities Occasional laxatives of the usual type certainly are not harmful Enemas or suppositories may be less disturbing to the digestive tract s function but impairment of anal sphincteric tone from excessive frequency may be a result

In conclusion the older gastrointestinal system is a complicated and possibly hyper reactive channel subject to inherent and reflected disturbances Its direction and correction require understanding based on careful examination

HORMONES

The indications and uses limitations and precautions of specific hormonal application in definite clinical deficiency states are the same in older persons as in younger ones However these metabolic reactors have multiple effects which can cause homeostatic disturbances that are less well olerated by the aging organism Projection f use from the limited and well-defined andular syndromes has led to major modi ations in therapeutics On the basis of controlled studies and unwarranted mises some endocrine preparations have n promoted as a form of therapy to the results of long term pathologic con ons The desire to rejuvenate or to re cize often has taken precedence over romotion of health cautions in the use of such hormones in the higher age group arise from the chemical changes incident to application Indiscriminate use is condemned as the list of complic from such medications lengthens interplay of forces that precede, a pany and follow the use of hormones be evaluated to preserve physiologic e librium *

ANESTHETICS

The development of the field of an thesia as a medical specialty has reduce hazards of the anaesthetics proportionally A physiologist at the head of the operating table as it has been stated so often can play a major role in surgical evaluation There is a cooperative arrangement for the selection of the agent to be used Surgical risk morbidity and mortality have shown progressive reduction as the application and nature of anesthetic agents are improved Regional intravenous spinal, and inhalation methods are well tolerated by the older individual Safeguards for the circulatory system and fluid balance have been elaborated not only for the course of the actual operative procedure, but as plan up to complete ambulation †

Diet‡

The average older age diet should contain about 25 calories per kilogram or approximately 11 to 12 calories per pound of body weight These figures must be adjusted to activity physical type disease states and other variables

Generally about 50 per cent of the total caloric intake should consist of carbohydrates 30 per cent fats and 20 per cent proteins Translating these percentages into food values a caloric intake of 2000 calories for an average 170-pound male

* See also Chapters 27 31
† See al › Chapter 41
‡ See also Chapter 32

tion of nutritional imbalance elimination of sources of blood loss and improved general hygiene cannot be replaced by wholesale application of hematologic agents Despite frequent need for these substances, it may be said generally that improper rather than proper use has been the more common state of affairs In definite need, the benefits are readily apparent although possibly a little slower in the older body The relief of symptoms such as dyspnea, angina or paresthesias is marked as the full nutritional benefit of an improving blood content is felt

ANTISPASMODICS

These drugs are used primarily to counteract hyperreactivity of smooth muscles They have selective parasympatholytic action, decreasing gastric secretion and gastrointestinal motility atropine having central stimulating as well as mydriatic effects Blurring of vision dryness of the mouth tachycardia mental confusion and even hallucinations may develop as occasional toxic reactions Glaucoma can be precipitated in older individuals sensitive to cholinergic agents Urinary retention may occur when there is prostatic enlargement In aging tolerance is limited and indications for use are less frequent than in younger mobile persons

When there is the possibility of unexpected distal effects, as mentioned these should serve as deterrents to dose and frequency of application or even contraindicate prescription of atropine and its derivatives Desired effects may be obtained by allied preparations the newer atropine like drugs possibly causing fewer side effects There are many conditions of smooth muscle spasticity in the geriatric group of patients for which the sympathetic blocking medications are necessary the precautions cited should not prevent proper application

STOMACHICS AND OTHER GASTROINTESTINAL MEDICATIONS*

These materials are of traditional value Bitter tonics have almost been displaced by compounded vitamin preparations The amount of increased value from the substitution has been questioned Use of hydrochloric acid in liquid or powdered form has been under critical survey Absorption of calcium salts, promotion of gastric antisepsis and control of some symptoms may serve as indications for use However there are many individuals with achlorhydria who are asymptomatic without such substitutes The indiscriminate use of carminatives, stomachics and digestive enzymatic adjuvants seems an outdated and rather empiric type of therapy but some elements of value in the symptomatic direction of individuals suggest that they should not be discarded too soon

Possibly no group of drugs are used more often on the basis of symptoms alone than proprietary digestive modifiers Pepsin pancreatin, antacids and acids usually are prescribed in inadequate dosage Alkalies buffering resins and other forms of antacids can affect electrolyte reserves and balances that may require compensation Considering the number of pathologic states associated with disturbances of gastrointestinal function correct diagnosis must precede the prescription It is little to be wondered that digestive distress secondary to genitourinary disease or to vascular ischemic states cannot be modified by medications aimed at one but caused by an *other condition*

Constipation

Older persons who have not been wrongly conditioned by family custom or overwhelmed by the impact of advertisements are not particularly subject to constipation The difficulty is usually carried over from younger years Change in bowel

* See also Chapter 17

42. Surgical Principles in Treatment

KEITH S GRIMSON

EARLY in the history of medicine surgery developed as a means of treatment of certain medical problems Hippocrates (460–370 B C) gave excellent descriptions of treatment of wounds use of dressings and handling of skull fractures but dreaded amputation of limbs By 1800 Galen Celsus Harvey Wiseman Hunter Morgagni and others had developed methods of reasoning and study and had made contributions in physiology anatomy and pathology which laid the background for rapid development in surgery Discovery of ether and chloroform early in the nineteenth century gave an added impetus Demonstration of Pasteur in 1856 of micro-organisms which caused wound infection and the institution by Lister in 1867 of antiseptic technics led to reduction of mortality rates which had approached 50 per cent for amputations

By 1887 Treves recommended removal of the appendix during the interval between attacks Courvoisier by 1890 had developed the background for accurate operations upon the gallbladder During the late nineteenth century and the first half of the twentieth general surgery and the surgical specialties evolved from their early minor role in medicine into a larger position generally equal in hospital patient bed occupancy to medicine and specialties It is inherent in this relative recent and continuously more diversifi development that principles of the surgic treatment of disease cannot be standardize and are subject to change with new developments

The purpose of this chapter is to discuss modern surgery briefly from the point of view of practical therapeutics In the interest of brevity and in keeping with the objectives set for this book diagnosis theoretical considerations details and references will be omitted Such information is available in current literature and is of course important Information presented in this chapter will consist of a practical running commentary on surgical therapy of wounds burns injuries and infections of the hand repair of hernia disorders of the gastrointestinal tract and of the liver biliary tract and pancreas tumors of the face mouth neck thyroid and breast operations on the heart pericardium thorax pleural cavity mediastinum and lung disorders of the lymphatic system and a discussion of surgery on the autonomic nervous system Single or

will consist of about 1000 calories or 250 Gm of carbohydrate, 600 calories or 66 Gm of fat, and 400 calories or 100 Gm of protein

Since many older individuals have a good appetite in the morning the day s food should be apportioned in proportions of 2/5, 1/5 and 2/5, or 2/5 1/5, 1/5 with the remaining fraction given as an accessory daytime or bedtime feeding

Even in the absence of specific patterns of vitamin deficiencies a biochemical avitaminosis may exist It is uncertain whether these nutritional elements are reduced because of increased requirements or reduced ability to absorb and utilize them Many older individuals tolerate single or multiple vitamins satisfactorily and more particularly when there are indications of general nutritional deficiency They must be evaluated as cooperative agents in many metabolic processes rather than as metabolic prima donnas

SULFONAMIDES*

Due to factors in conjugation renal excretion changes in acid base balance and hematopoietic effects cumulative toxic effects from the sulfonamides appear rather readily With reduced dosage increased time between doses and other precautions such as insuring a good renal output and maintenance of urine alkalinity these substances can be used beneficially They are too effective in application to be disregarded

ANTIBIOTICS†

Development of new forms of penicillin possibly having lessened antigenic qualities contributes to the margin of safety The same has been true of the later forms of streptomycin Aureomycin terramycin and chloramphenicol seem to produce more gastrointestinal disturbances in the older person and may permit oral, vaginal or rectal fungus overgrowth as their specificity affects normal bacteriologic balances

Synergistic properties among these several agents are being explored In some combinations there are antagonistic effects, and in others the effects of both are enhanced Generally, their use should be indicated specifically and controlled rigidly Most bad effects have been due to unwarranted prescription or sensitization which followed injudicious applications Others are due to disturbance of body mechanisms such as vitamin synthesis or changes in the bacteriologic environment

* See also Chapter 4
† *Ibid*

ANTICOAGULANTS*

The anticoagulant agents have a wide field of usefulness in the older individual Anatomic and physiologic characteristics increase the possibility of thrombotic and embolic events The frequency of pulmonary embolization and thromboembolic states is appreciated in most instances more by the pathologist than by the clinician The sharp rise in incidence from trauma, excessive recumbency postoperative conditions, cardiac impairment and local pressure effects as in long standing peripheral edema indicate the need for extension of the study and use of this therapeutic measure Exercise, mobilization supporting bandages and the use of every therapeutic adjunct lessen this common hazard to the older body Reliance on drugs with or without exercises must be adjusted to individual abilities

In older individuals smaller doses of these agents may be required to achieve control Return to normal levels requires a longer time after withdrawal of the drug Scrupulous precautions regarding use in hepatic renal hemorrhagic, and gastrointestinal ulcerated conditions are required

* See also Chapter 15

plastic technic Associated injuries of major arteries and nerves are repaired at the first operation but those of tendons at the time of secondary closure or later

The only exception to the general principle that a fresh, potentially contaminated wound can be converted into a closed clean wound occurs with human bites These are inoculated with pathogenic oral bacterial and in general should be treated as infected wounds

Infected Wounds Certain surface wounds in patients who do not—or because of circumstances cannot—seek prompt medical attention are available for treatment only after twelve hours or more has elapsed following the time of injury In general these must be considered infected wounds and treated conservatively Aseptic principles, however must be strictly enforced Hot wet compresses changed in an open ward by attendants not wearing masks usually do more harm than good since they expose wounds to infection by additional organisms Preferably these infected wounds are initially cleansed and then covered with a layer of petrolatum gauze, closed by a pressure bandage and subsequently examined only under aseptic conditions The general condition of the patient rather than the appearance of the wound is used as a guide to treatment Parenteral antibiotics or other chemotherapy are employed Often by the fifth or sixth day secondary debridement and closure will be possible

Immobilization

Immobilization of large wounds is important and can be accomplished by the use of bulky closed pressure dressings the use of partial or complete casts and by limitation of activity If primary closure has not been possible and the wound is closed by a layer of petrolatum gauze and a bulky dressing granulation and later scar tissue will form each day Early secondary closure or skin grafting will minimize the formation of scar tissue and yield the greatest final restoration of function

Ischemia of an extremity resulting from tight casts or bandages or from swelling of tissues within the tight fascial spaces particularly of the forearm, if neglected will lead to gangrene or at best, to fibrosis Volkmann s contracture of forearm and hand Toes and fingers extending beyond bandages should therefore be inspected routinely for the development of discoloration or numbness Casts, bandages and even fascial pressure should be released if necessary Interference with circulation may follow direct injury of major vessels If popliteal or brachial arteries are involved surgical exploration and repair is necessary

BURNS

Uniformity of opinion regarding local treatment of burns occurred as a result of studies of casualties treated after the Coconut Grove fire A military consultant committee for burns found the pressure bandage method developed by Koch and Siler superior to the tannic acid silver nitrate, triple dye, and other eschar forming technics

Pressure Bandage Method

Local Treatment As advocated by Koch *the burned surface is first gently* cleansed, repeated washings of soap and water and irrigations with saline being used A single layer of petrolatum gauze is then spread over the burned area Large dressings well padded by sterile machinist waste or other bulky loose material, are then applied Around these loose dressings an elastic bandage is wrapped to provide only gentle pressure Treatment is carried out in an operating room where aseptic precautions are used Bandages are left in position for ten days to two weeks unless

alternate forms of treatment will be recommended, depending on the degree of unanimity among surgeons Omitted from the author s presentation are details of treatment of diseases falling within the province of neurosurgery, orthopedics otolaryngology, ophthalmology, urology, proctology, and plastic surgery Nevertheless certain basic principles will be found common to practically all surgical problems The differences usually consist of special modification of these principles

Wounds, Burns, and Shock

WOUNDS

Major emphasis must be placed upon asepsis, antisepsis having been regarded since the days of Lister as of secondary importance Most serious infections or surface wounds are caused by human pathogenic bacteria sprayed from the oral cavity of those attending the patient or by airborne cross contamination occurring as wounds are opened or dressed in the hospital These infections are preventable

Tetanus*

Infection by the organisms of tetanus or gas gangrene is less frequent Tetanus antitoxin must be considered for every injured patient Fortunately prophylactic use of tetanus toxoid by pediatricians and by the armed forces has increased the number of immunized patients in whom danger of tetanus can be minimized simply by booster injection of toxoid which obviates the use of antitetanus serum

Because of the danger of sensitization each patient treated by antitetanus serum should receive two or three prophylactic toxoid injections so that if subsequently injured he may receive booster injections of toxoid rather than serum The incidence of infection with gas forming organisms can be kept to a minimum by proper debridement of necrotic tissue from wounds Serums antibiotics and chemotherapy are important for the treatment of gas gangrene and may be used prophylactically as an adjunct to the care of wounds Other organisms found in infected wounds are usually less virulent

Injuries. Most injuries are treated within the first few hours following trauma If the oral dissemination of bacteria is eliminated by the use of masks on attendants and the patient, potentially contaminated wounds can be cleaned with soap or detergents and water or saline solutions, necrotic tissue excised and the wounds then repaired and closed Any associated defects of nerves or arteries also may be repaired A contaminated wound thus may be converted into a clean closed wound Rarely, if ever should sulfonamides or antibiotics be placed in the wound for they injure tissue and promote inflammation and subsequent fibrosis However they may be given systemically Drains should be avoided whenever possible since they cause foreign body reaction Also they act as wicks and can permit the passage of bacteria into wounds

Because of loss of tissue certain wounds cannot be closed by approximating adjacent skin edges Skin grafts can be used occasionally to cover such wounds More often these open areas when cleansed are converted into closed wounds by placing sterile petrolatum gauze over the defect and encasing the injured part in a large sealed pressure bandage Five or six days later secondary closure is effected using

* See also Chapters 5 and 6

avoiding primary closure Repair of tendons may be accomplished as a secondary procedure after infection has subsided

Other traumatic wounds of the hand treated within the first six or twelve hours may be converted from contaminated wounds to clean wounds and primary repair of tendons and nerves undertaken, if necessary evulsion defects being closed by primary free or pedicle skin grafts

REPAIR OF INJURY

Divided extensor tendons severed as they travel along the dorsum of the fingers or hand usually are repaired easily with good results Evulsion of their insertion into the distal phalanx if complete requires reattachment by suture to avoid if possible, a flexion deformity baseball finger' Repair of severed flexor tendons particularly in the fingers less easily effects good function These tendons travel beneath fascial pulleys at the interphalangeal and metacarpal phalangeal joints At the metacarpal phalangeal joint the profundus and sublimis tendons are often injured together Smooth function through the pulleys is almost impossible if each tendon is sutured Good function can be achieved more consistently if a portion of the sublimis is removed as a free tendon transplant and inserted into the profundus distally at the level of the middle phalanx and proximally in the palm removing an inch or so of each divided end of the profundus The profundus tendon thus repaired alone will adequately flex the finger

Injuries or diseases of the tendon near a pulley may lead to snap finger or spring finger The tendon enlargement is pulled through the pulley by powerful flexor muscles and cannot be pulled back by the less powerful extensors When the finger sticks in flexion frequently and interferes with occupations such as typing surgery to enlarge the pulley or decrease the diameter of the tendon is indicated

INFECTIONS

Infections in the superficial parts of the hand, in the tendon sheaths or in the deeper fascial spaces may cause serious loss of function Usually these infections are caused by only one or few types of organisms When the infected area has been opened for drainage, asepsis must be rigidly enforced Lax technics such as hot wet compresses changed every few hours each change permitting exposure of the wound to secondary infection, may cause disastrous additions to the types of bacteria already present in the wound Similarly the use of rubber drains in any hand wound causes undesirable foreign body reactions and scarring of delicate tissues and sheaths and may cause further infection Therefore, pressure bandage technics and adequate incisions for drainage are imperative Certain infections of the hand however deserve special consideration

Superficial Infections

Superficial infections such as furuncles carbuncles and cellulitis should be promptly and carefully treated with rest local heat or insulating soft moist bandages, antibiotics, or chemotherapy and with incision and drainage only when localization has occurred Paronychia often require incisions in the adjacent soft parts with removal of part or all of the proximal portion of the nail

Felons cause intense throbbing pain and excruciating tenderness of the terminal phalanx of the finger These symptoms establish the diagnosis and indicate the need for immediate surgery One must not wait for superficial evidence of a localized inflammation Infection in the closed fascial space of the finger tip causes edema which early compresses arteries to the interior of the distal phalanx If acute ischemia is neglected aseptic necrosis of the phalangeal bone will occur and lead ultimately to sequestration (bone felon) The surgery

elevation of temperature or other systemic signs indicate infection Usually the closed pressure bandages prevent occurrence of secondary infection Also they immobilize the limb or area in an optimum position Grafting of skin, when necessary is done at the time of removal of the initial dressing or within a few days of removal to minimize development of scar tissue in the nonepithelialized burned areas

Pressure bandages are easily applied to burns of the extremities or trunk Those of the face or perineum are ordinarily treated by application of non-eschar forming jellies or ointments It must be emphasized that eschars around the face the rectum, or the genital organs restrict function and should be avoided Also eschar treatments applied to the hands cause constriction and associated ischemia of fingers and frequently lead to gangrene or ischemic contraction

Systemic Treatment Although there is agreement regarding the local treatment of burns there exist differences of opinion concerning the general treatment of the patient Antibiotics usually are used prophylactically though many insist that sulfonamides should not be employed because of the possibility of renal injury Pain usually is relieved by light anesthesia or narcotics during the local treatment of the burn

However, many recommend that drugs which depress respiration should be used sparingly for lack of oxygen may injure capillaries Some recommend routine administration of oxygen while others employ oxygen only in those patients who have respiratory difficulty following inhalation of irritating fumes

Recently pituitary adrenocorticotropic hormone (ACTH) has been advocated in the treatment of severe burns on the concept that circulating endogenous adrenocorticotropic hormone is quantitatively insufficient to meet the acute stress (Whitelaw) It has been established that grafting of skin can be accomplished in patients receiving ACTH Nevertheless much additional work must be done to determine whether a severely burned patient has a deficiency of ACTH or of cortisone and also whether administration of these preparations—which cause extensive physiologic metabolic and electrolyte changes—can be safely managed

A major part of the general treatment of the patient is prompt and effective management of shock The principles closely resemble those applying to shock from other wounds or injuries and are discussed in Chapter 43

Hand

SUCCESS in surgery of the hand with minimal loss of function depends upon the use of a strict aseptic technic and knowledge of the details of anatomy and of surgical principles available in books and published reports Particularly in the hand oral or air borne bacteria must be kept away from wounds by placing masks on the patient and attendants and performing all treatments with operating room care Pressure bandages are applied to cover the wounds prevent secondary infection and immobilize the part

Injuries caused by a human bite usually cannot be converted to clean wounds because of the virulence of the contaminating organisms and are best treated from the onset as infected wounds the operator

phragm occurs in children and requires reduction and repair Dislocation of the stomach into the thoracic cavity produces the so-called upside-down stomach Colon and small bowel also enter the thoracic cavity In adults this situation may be present as a result of gradual protrusion through a congenital weakness or of disruption following external violence or penetrating injury Usually these hernias also are repaired

HIATUS HERNIA

Hiatus hernias although often associated with symptoms of lower esophageal obstruction and occasionally with bleeding require repair only when symptoms are severe Crush of the left phrenic nerve may give relief particularly when the hiatus hernia is associated with a congenitally short esophagus It is often the initial treatment in old or debilitated patients When repair is indicated a transabdominal or a transthoracic approach can be used The author prefers a left transthoracic approach with incision through the diaphragm to permit repair below as well as above the hiatus

INTRA-ABDOMINAL HERNIA

Intra abdominal hernias are commonly discovered during exploratory laparotomy for obstructions of the bowel Presence of paraduodenal and some other hernias may be suspected however, by the roentgenologist Paraduodenal hernia occurs through the ligament of Treitz Other locations of internal hernia are in pockets or defects of mesentery or omentum, congenital or resulting from previous surgery The congenital varieties are often located about the terminal ileum cecum or ascending colon and may be associated with malrotation of the intestine Occasionally a hernia will occur in the obturator foramen

FEMORAL HERNIA

Femoral hernias should always be suspected in patients with intestinal obstruction or with unexplained peritonitis since not infrequently they are overlooked with serious results The opening of the sac is small and rigid a situation favoring strangulation Reduction and repair is indicated when diagnosis is established

POSTOPERATIVE HERNIA

Postoperative abdominal or so-called ventral hernias usually follow infection or unrecognized partial disruption of operative incisions Incidence of these hernias is reduced by the practice of avoiding drains in or through the main abdominal wound they are placed when possible through separate stab wounds When postoperative hernia occurs repair should be undertaken soon after the diagnosis is established since delay will permit further enlargement of the defect and the sac

Gastrointestinal Tract *

SURGERY of the gastrointestinal tract will be outlined from the pharynx downward consideration of organs draining into the intestine being left for later discussion

* See also Chapter 17

ESOPHAGUS

Pharyngeal or esophageal diverticuli produce difficulty during swallowing Forces of deglutition plus a congenital weakness or defect of the musculature, usually in the

immediately employed is an incision in the ulnar side of the involved distal phalanx This is deepened into the finger anterior to the palmar surface of the bone and divides the fascial investment and the radiating trabeculae Pus seldom will be encountered but the incision releases pressure An occlusive dressing with petrolatum gauze over the wound and no drain generally completes local treatment Rest and antibiotics or chemotherapy supplements the treatment

Tendon Sheath Infection

Acute tenosynovitis or infection of a tendon sheath is characterized by moderate swelling of the finger and excruciating pain with active and passive motion and during palpation along the tendon sheath These findings indicate the need for drainage One should not wait for evidence of localization but should proceed with a long lateral incision along the finger and into the web of the hand Infections of the thumb or little finger may extend along the radial or ulnar bursa into the wrist and require drainage Neglected tenosynovitis of the ring and of the index finger into the thenar space requires proper drainage of these spaces

Collar button infections of the web of the hand exhibit small abscesses superficial and deep to the palmar fascia Incision should drain both abscesses

Hernia

HERNIATION or protrusion of the contents of the abdomen through a weak spot a congenital or operative defect in the abdominal wall, or into a pocket within the abdomen occurs relatively frequently and usually requires operation to reduce the hernia and repair the defect Repair of small reducible superficial hernias by injection of sclerosing agents is attempted only by a very few surgeons

INGUINAL HERNIA

Inguinal hernias direct or indirect are most common In infants these hernias are congenital or indirect as a rule and are usually first treated by a yarn bandage or truss or by other support If they persist herniorrhaphy should be performed Some prefer elective herniorrhaphy during the first few months of life Incarcerated or strangulation hernias if not easily reducible require immediate surgery In adults occurrence of direct or indirect hernia is usually attributed by the patient to some particular strain or accident Development however, with few exceptions is gradual, the strain serving only to call the attention of the patient to the protrusion Unless some contraindication to elective surgery exists most surgeons recommend operation If contraindications to elective surgery exist —particularly in old people—a truss may be tried Local anesthesia is frequently used for herniorrhaphy

UMBILICAL HERNIAS

Umbilical hernias occurring in children often will disappear spontaneously following maintained reduction with adhesive strapping If reduction is not achieved or if umbilical hernia occurs in adults surgical reduction with repair of the defect is indicated

DIAPHRAGMATIC HERNIA

Herniation of adjacent abdominal viscera through a congenital defect in the dia

cardioplasty, a transabdominal plastic anastomosis enlarging the esophageal gastric orifice upward several inches to connect the fundus of the stomach with the esophagus through the normal sized segment and well into the dilated portion relieves the physiologic type of obstruction The operation permits ready drainage of the esophagus, and often within a year or two in the author s patients is followed by restoration of the dilated portion to normal size Some difficulty is experienced late after operation as a result of irritation by reflex of acid gastric digestive juice and occurrence of esophagitis or ulcer, at or above the site of anastomosis This produces stricture erosion or bleeding in occasional patients When secondary plastic operation is necessary the author has supplemented the anastomotic procedure by adding vagotomy and gastroenterostomy (Recently esophagocardioplasty with vagotomy and gastroenterostomy have been combined at the first operation for achalasia)

Fistulas

Esophageal tracheal fistulas or tracheoesophageal fistulas occurring in newborn are usually incompatible with life unless surgery is performed With few exceptions the upper esophagus ends in a blind pouch and the lower esophagus connects with the bifurcation of the trachea Swallowed food therefore regurgitates Gastrostomy is contraindicated since gastric feedings will regurgitate into the trachea Surgery is indicated during the first few days of life Usually an operative technic devised to separate the lower esophagus from the tracheal bifurcation and connect it to the upper blind end of the esophagus is employed Mortality is high

Esophageal varices will be discussed under cirrhosis of the liver

STOMACH AND DUODENUM

Surgery for lesions of the stomach and duodenum is frequently discussed in texts, medical journals and medical programs and therefore will be outlined only briefly in this chapter

Carcinoma

Carcinoma of the stomach occurs often and should be suspected in any patient with vague upper abdominal discomfort, nausea weight loss or melena The present low cure rate following surgery can be improved only by early diagnosis established by frequent examinations of gastric contents and of the stool supplemented by early and often repeated roentgenologic and gastroscopic studies

Treatment is radical surgical removal of most or all of the stomach the omentum and the adjacent lymph nodes Transthoracic or thoracoabdominal operations are advisable for lesions of the upper stomach and total gastrectomy is not infrequently necessary Removal of the lesion should be attempted unless technically impossible since although the cure rate for carcinoma of the stomach is low palliation or worthwhile temporary improvement often follows resection Surgeons frequently remove adjacent organs directly invaded particularly if the carcinoma is a locally invasive slowly growing variety and is not associated with widespread metastases Most believe that exploratory laparotomy is always or almost always indicated in spite of roentgenologic or gastroscopic impressions of inoperability Biopsy alone *occasionally establishes that the tumor is* a radiosensitive lymphosarcoma and may be treated by roentgen ray therapy if the lesion is inoperable In general radiologic therapy is considered of little value for most types of gastric malignancy since ir radiation sickness is severe and possible benefit from treatment unlikely

Gastric Ulcer

An ulcer of the lesser curvature of the stomach (magenstrasse) that by history of

posterior wall of the pharynx, cause herniation and the formation of pulsion diverticuli When one occurs, a sac forms and descends into the base of the neck or the upper chest Swallowed barium often permits visualization of the diverticulum as a sac located in the superior mediastinum Difficulty in swallowing and inability to maintain weight indicates need for surgical removal, usually accomplished by a one stage procedure Traction diverticuli occur in the thoracic esophagus presumably, though not always as a result of adhesions They are ordinarily small and seldom require surgery

Carcinoma

Carcinoma of the esophagus must be recognized early with fluoroscopy and esophagoscopy and given prompt surgical treatment Delay greatly increases the likelihood of extension and inoperability Radiation treatment is generally considered ineffective and would cause delay Lesions of the pharynx and of the cervical esophagus are treated by radical excision including removal of adjacent lymph nodes and plastic reconstruction if possible

Lesions of the upper third or half of the thoracic esophagus are currently treated by excision with restoration of continuity accomplished by mobilizing the stomach into the chest and anastomosing it to the divided end of the upper esophagus The mortality from operation and likelihood of recurrence increase the closer the lesion occurs to the pharynx Few patients are ultimately cured The author therefore prefers transthoracic esophagectomy without restoration of continuity (the Torek operation) for lesions of the upper third of the esophagus This operation leaves the patient with a high cervical esophagostomy and a gastrostomy However, the mortality risk of this procedure is low and the surgical excision can be radical

Restoration of continuity in these patients not showing recurrence after a few years can be accomplished by subcutaneous mobilization of the jejunum from the abdomen and anastomosis to the remnant of the cervical esophagus

Carcinoma of the lower third or half of the esophagus or of the upper portion of the stomach is treated by transthoracic resection with direct anastomosis between the esophagus and stomach as described by Phemister or by larger thoracoabdominal incisions and similar anastomosis described more recently by several authors

Stricture of the Esophagus

Stricture of the esophagus—usually caused by swallowing lye or an acid—ordinarily can be treated by direct esophageal dilatations or retrograde dilatations through a gastrostomy Occasionally they require construction of an external esophagus or resection of the area of stricture continuity being restored by direct anastomosis to mobilized stomach or jejunum

Achalasia

Achalasia, also commonly but less appropriately termed cardiospasm or megaesophagus is apparently a failure of proper function of the esophageal gastric orifice and of the lower several inches of the esophagus Some describe absence or destruction and fibrosis of the myenteric plexus in this normal sized but abnormally functioning lower segment of the esophagus Accumulation of food and secretions above the poorly functioning segment eventually produces distention of the thoracic esophagus with marked enlargement and hypertrophy Mucosal erosions may cause hemorrhages Serious dysphasia and weight loss indicate the need for surgical treatment

Esophagoscopy and dilatation of the short lower segment and orifice should be tried and may effect some relief of symptoms but rarely decrease of the dilatation Esophago

Duodenal Ulcer

Duodenal ulcer resistant to medical management may require surgery because of intractable pain repeated massive hemorrhages uncontrollable acute hemorrhage obstruction or medical invalidism Patients sometimes are not able to work or live a satisfactory life on the strict medical program necessary for control of their ulcer

Gastroenterostomy the earliest surgical supplement to medical management of ulcer was so frequently followed by occurrence of jejunal stoma or marginal ulcer that it is now abandoned as a treatment by most surgeons and is used only occasionally by some for elderly patients without great hyperacidity

Subtotal gastric resection by which the antrum is removed and the duodenum excluded theoretically eliminates the gastric or chemical phase of digestion It also removes the active peristaltic activity of the antrum Alkaline duodenal content and bile are regurgitated into the stomach through the anastomosis and aid neutralization Subtotal gastric resection thus decreases hypermotility and hypersecretion two important causes of ulcer This procedure is currently the most popular surgical treatment of ulcer According to numerous reports it is accomplished with an operative mortality rate varying from slightly over 5 per cent in many hospitals to less than 1 per cent in some clinics (Wangensteen) The reported incidence of jejunal *ulcer following* resection has varied from insignificant to higher than 7 per cent Ulcers are particularly likely to recur in patients whose primary difficulty was gastrointestinal hemorrhage

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the remaining 20 per cent is caused by failure to gain or maintain weight and strength occurrence of anemia development of the so-called dumping syndrome or recurrence of ulcer with distress requiring dietary and medical *management*

Vagotomy Recognized limitations of subtotal gastric resection *for duodenal ulcer* have stimulated search for new treatments. In 1942 Dragstedt revived *interest in* vagotomy resection of the two vagus nerves and their plexus about the lower esophagus as a surgical treatment for duodenal ulcer This operation usually reduces volume and acidity of gastric secretions and decreases or alters gastric motility It abolishes the cephalic or psychic phase of digestion and particularly reduces the excessive secretions of ulcer patients during the night hours.

Dragstedt has since used vagotomy with and without gastroenterostomy as a substitute for gastric resection The author employed transthoracic vagotomy alone for duodenal ulcer in 1944 and 1945 but because of frequent occurrence of faulty function of the outlet of the stomach following denervation with associated obstruction retention of gastric content and distention of the stomach abandoned this procedure in favor of vagotomy routinely combined with gastroenterostomy *In our series* the incidence of recurrence of duodenal ulcer following vagotomy *alone* was around 10 per cent Moore also noted a high incidence of recurrence of ulcer following vagotomy alone In the experience of the author and many others vagotomy with gastroenterostomy has produced results as satisfactory *as or better than those from resection* This has been accomplished with a mortality risk generally less than 1 per cent and with infrequent occurrence of jejunal ulcer

Side effects of vagotomy and gastroenterostomy are occasional failure to regain normal weight occasional occurrence of diarrhea and more frequently minor complaints of a sensation of epigastric fullness or of weakness after eating looseness of stool or bowel cramps Two patients in the author s series experienced severe cramping abdominal pain and had tarry stools Ex

symptoms, roentgenologic characteristics, study of gastric secretions, gastroscopic and other examinations is apparently a gastric ulcer, nevertheless, may be a malignant neoplasm Statistics indicate lesions 2–3 cm in diameter are benign ulcer about four times in five Carcinoma is occasionally demonstrated in a gastric ulcer present by history and record as long as five or ten years

Surgery for gastric ulcer is indicated at the time of diagnosis or following several weeks of carefully controlled medical management and failure of complete healing Some believe (Lahey) that all gastric ulcers should be promptly treated by subtotal resection if technically possible, or by total gastrectomy if necessary The operative risk and postoperative nutritional difficulties inherent in total gastrectomy lead others to believe that subtotal gastric resection is the treatment of choice for lesions of the distal half or two thirds of the stomach and juxtaesophageal ulcers should be treated by subtotal resection distal to the ulcer and leaving it in place or by vagotomy (Dragstedt) or vagotomy and gastroenterostomy (the author) Such conservatism spares approximately 4 patients in 5 who had benign ulcers from total gastrectomy but inadequately treats the fifth patient whose ulcer is malignant Each patient with gastric ulcer treated by vagotomy and gastroenterostomy or by distal resection should be carefully followed and if complete healing does not occur a planned radical operation for tumor can then be executed

Since there are few chances of curing high gastric malignancies this policy of conservative treatment of high gastric ulcer decreases the mortality risk and disability of the great majority of patients who have benign lesions and therefore seems justified Most surgeons believe that gastric ulcers located in the antrum or media should be removed by subtotal gastric resection

Prolapse of Gastric Mucosa

Prolapse of gastric mucosa into the duodenum, which causes pain or vomiting, bleeding and other symptoms, is being recognized more frequently as a result of increasing interest and perfection of diagnostic technics by roentgenologists and gastroenterologists Symptoms may be serious and require operation because of pain, weight loss, or bleeding The usual treatment is enlargement of the opening between the stomach and the duodenum by a pyloroplasty A minimal subtotal resection or an exclusion procedure has been employed by the author where a nodule of aberrant pancreas or a polyp is associated with the prolapse Either procedure affords gratifying relief of symptoms

Diverticuli of Stomach

Diverticuli of the stomach are rare but can occur and produce upper abdominal gastrointestinal symptoms which often resemble ulcer Their walls are extremely thin Although medical management is usually employed the diverticulum can be removed readily by surgical intervention In the author s experience exploration has not revealed evidence of ulcer for which the patients were formerly treated medically

Polyps

Polyps occurring in the stomach may be treated surgically because of bleeding or because of suspected malignant degeneration Frequently however they appear benign and are numerous throughout the stomach One or a few polyps can be removed through an incision in the stomach the mucosal base of each being sutured Complete removal of multiple polyps, however often would require total gastrectomy, a procedure apparently not warranted unless malignancy is present Removal of larger polyps or subtotal gastrectomy may be done and the remaining polyps examined roentgenographically or gastroscopically at regular intervals

Pyloric Stenosis

Congenital hypertrophic pyloric stenosis occurring in infants is associated with a localized thickening of the muscularis of the outlet of the stomach Operation (Fredt Rammstedt) consists of splitting the serosa and muscularis of the involved area and separating it by blunt dissection until obstruction is relieved and thin gastric mucosa bulges into the incision

Diverticuli of the Duodenum

Diverticuli of the duodenum occur not infrequently However they seldom produce symptoms requiring intervention Surgical procedures employed include careful excision and repair with detailed attention being paid to location of the closely adjacent common bile and pancreatic ducts

Other conditions affecting the duodenum such as reduplication cysts congenital atresias and obstructions are rare but when present often require surgery Carcinoma of the duodenum is also rare Malignancies of this area will be included in the discussion on the liver biliary tract and pancreas

Obstruction of Small Intestine

Obstruction of the jejunum or ileum associated with colicky abdominal pain distention and vomiting is probably the most frequently occurring disorder of the small intestine encountered by the surgeon Treatment may be conservative long tubes (Miller Abbott) being passed to the point of obstruction to effect suction decompression or operative laparotomy being necessary as soon as the condition of the patient is improved by use of blood and plasma or saline

Conservative suction intubation may be employed where signs of an acute abdomen (rigidity leukocytosis and fever) are absent and when previous operations or intra abdominal inflammatory processes have occurred indicating the probable presence of multiple adhesions or of localized inflammation Position of the tube and extent of decompression of the small intestine should be controlled carefully by roentgenographic examination If decompression is well established within twenty four or forty eight hours and the cause of obstruction is evident as in patients having recurring episodes of obstruction as a result of postoperative adhesions intubation may be the only treatment necessary

Treatment of obstruction of the small intestine is operative when signs of an acute abdomen exist or develop during intubation Peritoneal irritation under these circumstances suggests interference with circulation and loss of viability of distended gut with danger of perforation and peritonitis Examples of lesions which must be treated promptly by operation are volvulus strangulated hernia intussusception and mesenteric thrombosis Tumors cysts and a variety of other conditions also may produce obstruction

Diverticuli

Diverticuli of the small intestine may occur singly or there may be a few or many Surgery may be indicated because of obstruction strangulation or bleeding Single or several diverticuli can be removed but multiple diverticuli are treated with difficulty since they cannot all be removed and the one responsible for the bleeding cannot always be ascertained

Meckel s Diverticulum A Meckel s diverticulum usually suspected because of bleeding obstruction unexplained abdominal pain or a right lower quadrant inflammation not caused by appendicitis is ordinarily found incidental to abdominal exploration and easily removed

Mesenteric cysts caused by congenital reduplication of the small intestine leaving a blind segment or by developmental processes such as accumulation of chyle (chyloma) may be felt as movable abdominal masses or may cause obstruction and should be removed by operation

ploration revealed intussusception of the ileum without strangulation Increasing knowledge of diagnosis and treatment of the side effects of vagotomy has made their occurrence less frequent and less troublesome Side effects are most frequent during the first few months or year or two following operation after which symptoms usually cease or diminish in severity Although Dragstedt, the author of this chapter, and others prefer vagotomy and gastroenterostomy as a surgical treatment of duodenal ulcer and are continuing with studies the majority of surgeons continue to prefer subtotal gastric resection

All surgeons agree that the emergency operation for persistent massive hemorrhage from a bleeding duodenal ulcer should be excision of the ulcer with subtotal gastric resection and that the operation for perforation is repair and suture For duodenal ulcer with obstruction or pain either vagotomy and gastroenterostomy or subtotal resection may be employed depending upon the preference of the surgeon If the ulcer is active and induration of tissues exists at the time of surgery resection might be difficult and it would seem logical that vagotomy and gastroenterostomy be the procedure of preference Since hemorrhage occurs rarely after vagotomy and gastroenterostomy and not infrequently after resection the operation of preference for patients treated during an interval after hemorrhage would be vagotomy and gastroenterostomy

Jejunal, Stoma or Marginal Ulcer

Jejunal stoma or marginal ulcer produces *symptoms of lower abdominal pain* bleeding and occasionally obstruction Jejunal ulcer may follow gastroenterostomy alone or subtotal resection and anastomosis Although roentgenologic examinations and gastroscopy can demonstrate presence of

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tion of the colon usually develop slowly during several days Partial obstruction can be relieved by enemas or cathartics during preparation for a planned operation at the site of obstruction Complete obstruction *requires emergency surgical intervention by* proximal colostomy or infrequently cecostomy Until drainage is provided the colon proximal to the point of obstruction distends and its content cannot readily regurgitate through the ileocecal valve Intubation decompression through the small intestine is therefore of minor aid Unless distention is relieved by surgery rupture of the cecum usually will occur

Carcinoma

The cure rate of carcinoma of the colon by surgery is relatively high It is not a radiosensitive tumor and early diagnosis and operation are imperative Carcinoma of the cecum usually causes bleeding and anemia More distal carcinomas although they bleed usually produce obstructive symptoms, often with intermittent diarrhea and constipation

Malignancies of the cecum ascending colon and hepatic flexure are removed in one stage by resection of the right colon and *anastomosis of the terminal ileum to the* transverse colon Malignancies of the transverse, descending and upper sigmoid colon are often removed in one stage and a distal anastomosis is made, by which continuity is restored However, many surgeons prefer a two stage Mikulicz type of procedure, particularly where resection must be radical and blood supply compromised Under these circumstances an *open loop nonob*structive technic has advantages Malignancies of the lower sigmoid colon and upper rectum commonly are treated by a Miles type of combined abdomino perineal resection with removal of the rectum and permanent colostomy A few prefer resection of the sigmoid colon and rectum to the anus and restore continuity by a pull through procedure (Babcock, Bacon) which preserve the anus and its sphincter control The author is of the opinion that this procedure is worthwhile in selected cases *with smaller carcinomas of the lower sigmoid or upper* rectum

Ulcerative Colitis

Nonspecific ulcerative colitis is often a serious disorder *Development of extensive* ulceration with occurrence of fibrosis and multiple obstructions of the colon and debilitation of the patient make surgery imperative in advanced forms of this disease Colectomy with a permanent ileostomy and a suprapubic sigmoidostomy designed to become a mucous fistula is often necessary Occasionally secondary resection of the mucous fistula, lower sigmoid colon and rectum are required later In the presence of advanced stages requiring this form of treatment patients may later develop progressive involvement of the ileum which subsequently leads to malnutrition and death

It is most important, therefore, that these late stages of nonspecific ulcerative colitis be avoided if possible In the absence of any specifically effective chemotherapeutic agent or antibiotic and since other medical *forms of therapy are frequently ineffective* many surgeons advise ileostomy with exclusion of the colon early in the disease process Plastic appendage ileostomy (Dragstedt) can be performed and will protect the patient from uncomfortable excoriation of the abdominal wall Earlier performance of ileostomy evidently can diminish the number *of colectomies necessary* However *rarely, if ever does the colon heal* completely

In recent years vagotomy has been tried for ulcerative colitis (Dennis) in the hope of abolishing the gastrocolic reflex and of otherwise altering secretions and motility It is difficult to evaluate this procedure at the present time

Ileitis

Ileitis inflammatory thickening of a portion or portions of the small intestine, may involve the terminal ileum (terminal ileitis) or may involve one or more areas of the ileum or the jejunum (regional enteritis) with segments of normal bowel between (skip areas)

Terminal Ileitis The conventionally preferred treatment of chronic terminal ileitis is exclusion obtained by dividing the normal ileum above the affected area and connecting the proximal segment to the transverse colon Resection of the involved area was once popular but is now less frequently employed since recurrence rate seems higher after this procedure

Regional Ileitis Regional enteritis occurring in an acute stage and producing signs of an acute abdomen requires exploration by surgery to establish the diagnosis However according to most authors the inflamed segment of bowel should not be resected in the acute stage Chronic regional enteritis may require surgery because of obstruction diarrhea or other symptoms Conventionally, involved areas are resected restoring continuity by end to-end anastomosis The author has employed with satisfactory results a Roux procedure by which the small intestine is divided above the involved area and the proximal end connected to the bowel below the diseased area with an end to side anastomosis this leaves the diseased area excluded but otherwise undisturbed With terminal ileitis and regional enteritis there is a high incidence of recurrence or extension and some patients eventually lose so much small intestine by disease or operation that malnutrition and death eventually occur

Mesenteric Thrombosis

Mesenteric thrombosis should be suspected in patients with abdominal pain with a disproportionate degree of shock or vasomotor collapse, it is treated by resection of the devitalized segment of bowel Because of danger of further extension anticoagulants such as heparin and ' dicumarol often are started after operation

APPENDIX

Appendicitis is usually associated with obstruction of the lumen of the appendix, which causes distention, thrombosis of vessels, gangrene and perforation Infection by normal gastrointestinal flora probably plays an important but secondary role Accordingly, appendectomy should be the primary treatment with antibiotic and chemotherapy secondary

All agree that appendectomy should be performed early before rupture and peritonitis have occurred Most agree that the appendix should be removed and drains inserted when the patient is seen at a later stage and there is evidence of peritonitis In these patients gastric intubation and suction prior to and following operation is important since peritonitis produces ileus and intestinal distention must be prevented A minority feel that appendicitis with peritonitis should be treated by intubation alone Peritonitis with appendicitis is often encountered among young children or in the aged Early diagnosis of appendicitis in these age groups is difficult

All surgeons agree that a localized appendiceal abscess should be treated conservatively if it is palpable and not associated with generalized abdominal tenderness indicating peritoneal irritation Such abscesses usually drain spontaneously often evacuating into the cecum Only rarely will they extend further or cause debilitation of the patient and require drainage However, within one or two months after healing of an appendiceal abscess an appendectomy must be performed for otherwise there would be recurrence

COLON

Symptoms of colicky pain, distention and vomiting occurring with complete obstruc

This situation however occurs rarely in jection methods are misused so often with *resulting complications* that they are in dis repute among surgeons Carefully employed dissection and suturing with avoidance of cautery can effect complete removal of abnormal hemorrhoidal tissue without stric ture or other complications with minimal discomfort and with good assurance against recurrence This technic is applied com monly to all problems of combined internal and external hemorrhoids and frequently used for internal hemorrhoids alone Fre quently dissection must be continued com pletely around the rectum

Prolapse of the rectum if not extensive may be treated by an amputation technic Extensive prolapse however, is better treated by laparotomy with mobilization of the sigmoid colon and rectum and reattach ment in an elevated position within the ab *domen*

Liver, Biliary Tract, and Pancreas

ABSCESS OF THE LIVER

Abscesses of the liver may be large dis crete or loculated or they may be multiple Large abscesses may be localized by roent genograms obtained several hours or three or four days after intravenous injection of thorotrast (Reeves) Also they may be lo calized by probing with a long aspirating needle *If the abscesses are of amebic origin* operation and open drainage with its at tendant risk of secondary infection is avoided if possible (Ochsner) Repeated as pirations are recommended and emetine hy drochloride is administered systemically If the liver abscess is caused by other organ isms open drainage is indicated all possible precautions against secondary infection being employed

CIRRHOSIS OF THE LIVER

Cirrhosis of the liver often is recognized first by occurrence of complications of por *tal hypertension* particularly ascites and bleeding from esophageal varices The most common cause of ascites or of bleeding esophageal varices is *Laennec's cirrhosis* Other forms of cirrhosis and other unex plained disturbances of the portal circula tion are however frequent *Esophageal* bleeding also may follow thrombosis of the splenic vein

Numerous operations have been tried for portal hypertension usually with temporary or limited success Splenectomy alone or with other procedures has been most frequently employed since this operation elim inates as much as a third of the arterial in flow into the portal venous system Until recently splenectomy was usually combined *with an omentopexy (Talma) to bring* the omental veins in contact with subcutaneous or other extraportal veins Benefit may be obtained particularly in those patients *with* slowly progressive forms of the disease and without enormous ascites or severe nutri tional deficiency and hypoproteinemia Risk from this operation is not great

Splenectomy with portacaval anastomosis or portacaval anastomosis alone has been tried using several technics (Blakemore) Operative mortality rates of 18–50 per cent have been reported Currently direct anas tomosis of the portal vein with the vena cava is preferred to splenectomy and anas tomosis of the splenic vein to the left renal vein Recently ligation of the hepatic and *splenic arteries* (Rienhoff) has been intro duced and encouraging preliminary results are reported There is no agreement now *concerning indications* for operation tech nics or results

Some patients with little or no ascites

Diverticulitis

Acute diverticulitis of the colon may lead to localized peritonitis which may subside during observation and nonoperative treatment It may however, produce generalized peritonitis resembling that occurring with appendicitis Then exploration of the abdomen followed by placement of a drain to the site of the inflamed diverticulum is common practice More chronic diverticulitis may cause partial or complete obstruction If conservative treatment fails proximal colostomy is indicated Rarely a localized area of diverticulitis may be resected Usually however this is done because of a mistaken diagnosis of carcinoma

Polyps

Polyps occurring in the rectum or lower sigmoid may be removed surgically with a rectal or proctoscopic approach Isolated polyps in the more proximal colon if apparently benign require laparotomy and removal by opening and working through the colon if malignancy is suspected segmental resection of the colon and end to-end anastomosis is indicated Familial multiple polyposis may occur Patients with this disease usually develop malignancy and colectomy is indicated when a diagnosis is established Some surgeons also remove the lower sigmoid and rectum leaving a permanent ileostomy Others remove all of the colon except that readily accessible to the proctoscope performing a low ileosigmoidostomy and preserving rectal function Repeated proctoscopic examinations for evidence of malignancy and for snare removal of larger polyps are necessary during the lifetime of the patient if this procedure is used

Megacolon

Megacolon or Hirschsprung s disease usually produces symptoms early in life Most patients with this disorder can be treated by nonoperative methods and many have few symptoms in adult life Sympathectomies reported as beneficial by several surgeons are in the opinion of the author and others contraindicated Occasionally obstruction or perforation may require colostomy or exteriorization of part of the colon Usually however in the few patients requiring surgery a planned colon operation is possible

The earliest operations were segmental colon resections The author introduced colectomy and ileosigmoidostomy employing the procedure only for those patients with enormous dilation of all the proximal colon and upper sigmoid terminating in an area of normal sized lower sigmoid colon and a normal rectum This operation permitted liquid ileal content to enter the normal sized although abnormally functioning lower sigmoid and rectum

More recently Swenson has advocated removal of the rectum and lower sigmoid using a pull through procedure to bring the dilated gut to the anus He has employed this operation for the sigmoid achalasia variety of megacolon Reports indicate that patients with enlargement limited to the descending and upper sigmoid colon have done well on medical management alone and this is confirmed by the author s experience The pull through operation nevertheless is applicable to the more serious type of megacolon for which colectomy was recommended and is theoretically better since the normal sized lower sigmoid and rectum seem responsible for the abnormal function and proximal dilation Further studies and additional patients seem necessary to permit final appraisal of the advantages and disadvantages of colectomy and the pull through procedure

Hemorrhoids

Hemorrhoids commonly require surgical attention One or a few moderately large internal hemorrhoids if not associated with external hemorrhoids may be treated successfully by injection of a sclerosing agent

so later completeness of the operation may be determined by retrograde cholangiograms Carcinoma of the common duct, the ampulla of Vater, or the pancreas can be removed by pancreatoduodenectomy (Whippel, Brunschwig) preferably performed with implantation of the pancreatic duct in the intestine Palliative operations such as cholecystenterostomy or cholecystgastrostomy often involve a higher mortality rate and seldom achieve worthwhile prolongation of life or relief of symptoms

PANCREATITIS

Acute

Acute pancreatitis with severe upper abdominal and back pain and elevation of blood amylase is usually caused by an acute interstitial or edematous process and less often by the more frequently fatal acute hemorrhagic or necrotizing disease Primary attention in either condition should be given to the treatment of shock Many surgeons believe that operation should be avoided in early stages of the disease and reserved for late complications such as sequestration of pancreas and formation of pseudocyst Others believe that a small incision should be made over the gallbladder to determine the nature of the pathology and to establish drainage of the gallbladder and diversion of bile to the exterior

Cholecystostomy offers the advantage of permitting cholangiograms in patients recovering from pancreatitis so that stones if present in the common duct can be removed Theoretically reflux of bile into the pancreas is a cause of pancreatitis and diversion of bile by cholecystostomy may minimize further reflux

An alternate newer surgical technic shows *promise Since patients* with acute pancreatitis have severe pain and since visceral pain is conducted by afferent nerve fibers traveling along the splanchnic nerves bilateral splanchnic block with procaine administered paravertebrally through long needles relieves pain The general condition of the patient is improved remarkably and authors postulate that reflex vasospasm in the inflamed area can be relieved with a favorable effect on the disease process by use of splanchnic block Recent studies (Shingleton) indicate that intramuscular injections of 100 mg of methantheline bromide (banthine) reduce the external secretions of the pancreas and favorably influence the course of patients with acute pancreatitis

Chronic

Chronic or recurring pancreatitis is usually associated with deposits of calcium in the pancreas This form of pancreatitis does its harm by producing continuous or frequently recurring pain which may lead to morphine addiction or alcoholism It seldom causes diabetes jaundice or steatorrhea Pancreatectomy was the original surgical treatment but carried an appreciable operative risk and aggravated the tendency toward diabetes and steatorrhea Posterior splanchnicectomy in one or two operations (Smithwick) or exploratory laparotomy and transabdominal bilateral celiac and superior mesenteric ganglionectomy (the author) are now more popular treatments They interrupt visceral pain pathways without disturbing the pancreas

PANCREATIC CYST

Cysts of the pancreas may follow trauma or acute pancreatitis and develop without an epithelial lining These are called pseudocysts They may also originate as true cysts with epithelial lining Pseudocysts are often treated by marsupialization but when possible *should be excised True* cysts should be excised if removal is technically feasible since there is a chance that they may be malignant Either type is treated by some surgeons by internal drainage which is accomplished by anastomosis of the cyst to the intestine

present themselves for examination because of recurrent bleeding from esophageal varices For these patients resection of the lower esophagus (Phemister), resection of the lower esophagus with vagotomy and gastroenterostomy (Grimson), or gastrectomy (Wangensteen) has been performed Also employed by some are injection of esophageal veins with sclerosing solutions This is done either through an esophagoscope or through a transabdominal approach Acute hemorrhage from esophageal varices has been treated by the application of various forms of intraesophageal packs made of hemostatic sponges or by tamponade, using a special balloon

For patients whose primary difficulty is ascites attempts have been made to establish communication between the abdominal cavity and the subcutaneous tissue the venous system, or the ureter These operations have failed usually

Needle biopsies of the liver with special needles or trochars inserted through the abdominal or chest wall (Iverson and Roholm) after a local anesthetic have been used to establish the diagnosis and nature of hepatic diseases

CHOLECYSTITIS AND CHOLELITHIASIS

Cholecystitis and cholelithiasis are common surgical disorders Most evidence indicates that occurrence of inflammation of the gallbladder is primarily related to concentration of bile and associated chemical inflammation of the gallbladder resulting from irritation by bile pigments Also precipitation of these pigments and of cholesterol and excretion of calcium by the gallbladder is the primary cause of gallstones Obstruction of the cystic duct plays an important role in these inflammatory processes Infection plays a minor role since bacteria often are not present in acute cholecystitis

For this reason treatment of cholecystitis by surgery rather than by use of antibiotics or chemotherapy should receive primary consideration During the first two days of an attack acute cholecystitis is treated by the surgeon performing an emergency cholecystectomy If an attack has lasted longer than two days nonoperative treatment is commonly used, cholecystectomy or cholecystostomy being reserved for emergency complications such as gangrene, perforation, and empyema Inflammatory reaction of adjacent tissues at this stage often makes cholecystectomy difficult Most patients seen two days after onset of an episode of acute cholecystitis will respond to conservative treatment and may have cholecystectomy later Although the principle of performing a cholecystectomy early in an attack is popular some surgeons believe that acute cholecystitis should be treated conservatively and that cholecystectomy should always be reserved for an interval stage

CHOLANGITIS

Cholangitis characterized by chills and fever and usually by jaundice is often associated with a common duct stone which intermittently obstructs the flow of bile Removal of the stone and the diseased gallbladder is indicated

JAUNDICE

Obstructive jaundice caused by a stone in the common duct usually is differentiated from that associated with carcinoma by a history of recurring episodes of colic and by absence of distention of the diseased and fibrosed gallbladder Jaundice with carcinoma ordinarily develops without pain, deepens steadily and is associated with distention of a normally elastic gallbladder (Courvoisier s law) Either condition requires surgery after careful preparation of the patient including the administration of a vitamin K product Following removal of stones most surgeons leave a catheter in the common duct through which a week or

Adenoma

Nontoxic adenomas of the thyroid, whether diffuse, nodular, or discrete gradually increase in size and disfigurement Also, there is some danger of malignant degeneration Most surgeons agree that unless cardiac or other contraindications exist these tumors should be removed

Thyrotoxicosis

Thyrotoxicosis with or without goiter is generally considered a surgical problem Following adequate preoperative preparation with iodine or with propylthiouracil or methylthiouracil followed by iodine, most surgeons agree that extensive removal of the thyroid gland is indicated Careful dissection accomplishes adequate removal of thyroid tissue with little risk of injury to the recurrent laryngeal nerve or to the parathyroid glands Recurrence of thyrotoxicosis following adequate removal is infrequent Radioactive iodine is being studied as an alternate treatment and may be of value in patients who are poor risks surgically

Carcinoma

Carcinoma of the thyroid gland must be proved by biopsy and careful histologic study If present radical surgical removal including adjacent lymph nodes is indicated Radioactive iodine is often a valuable alternate treatment for inoperable lesions or when recurrence follows surgery

Breast

CARCINOMA

A patient with carcinoma of the breast is treated by the surgeon performing a radical mastectomy and removing the axillary lymph nodes The surgery is followed by a course of localized irradiation Sterilization of a patient by irradiation or removal of the ovaries is of doubtful value as a supplementary measure If inoperable metastases are present local irradiation has palliative value Androgen therapy (testosterone) or in the elderly patient well past the menopause estrogen therapy may effect further palliation particularly relief of pain and retardation or regression of metastases Fortunately, the cure rate following early diagnosis and radical mastectomy is relatively high

CYSTIC MASTITIS

Chronic cystic mastitis which occurs frequently produces palpable nodular irregularities in the breast and is characterized by hyperplasia, fibrosis, and cyst formation Although it produces discomfort, particularly during menstruation the greatest concern to patient and physician is malignant degeneration The incidence of malignant neoplasms in patients with this disorder is variously reported as less than 1 per cent and more than 3 per cent

Biopsy or excision of localized firm areas is often indicated Aspiration of cysts without biopsy may be substituted for excision of cysts providing a tumor mass is not palpable when the cyst is empty Every patient with chronic cystic mastitis must be examined at regular intervals A decision concerning choice of patient or choice of area for treatment by excision biopsy or aspiration is difficult and is a matter for the individual judgment of the surgeon Bilateral simple mastectomy for chronic cystic mastitis is warranted only rarely

Many discrete firm benign tumors (e g adenofibroma) occur in the breast Surgeons

Face, Mouth, Neck, and Thyroid

CARCINOMA

Basal cell carcinoma of the skin of the face can be treated successfully by irradiation therapy Most surgeons interested in plastic surgery however, prefer primary excision followed by plastic closure or skin grafting This has an advantage since some lesions recur after irradiation treatment and others have mixed basal and squamous cell components

Small squamous cell carcinomas located in readily accessible areas also can be treated successfully using irradiation therapy Most surgeons prefer however radical excision of the primary lesion performing during the same operation or subsequently excision of all lymph nodes to which drainage may have occurred For lesions of the buccal cavity this occasionally requires bilateral radical neck dissection Lesions inaccessible to surgery are treated by roentgen ray therapy radium or implantation of radon seeds or needles

Biopsies of all lesions of the face and mouth should be made because nonmalignant tumors or inflammatory processes occur and may require forms of treatment other than irradiation or surgery

Salivary Glands

Tumors or inflammatory processes of the *salivary glands often cause difficulty* Mixed tumors of the parotid gland are usually benign Simple excision from the parotid *gland is associated with some hazard of* injury to the facial nerve or its branches particularly the inferior mandibular Also recurrences occur Therefore many surgeons prefer complete excision of the parotid gland associated with careful dissection visualization and preservation of the facial nerve and its branches (Blair) In the author's experience this has been a satisfactory procedure Tumors of the submaxillary and sublingual glands are less frequent Firm enlargement of these glands is more often caused by a chronic inflammatory process In either event, however, biopsy or surgical removal is indicated

Branchial Cleft Cysts

Branchial cleft cysts should be removed surgically Diagnosis can be confirmed by *aspirating the contents If a cyst is* large repeated aspirations during several days before operation will reduce its size and simplify removal

Thyroglossal Duct Cysts

Thyroglossal duct cysts or sinuses should be removed completely It usually is necessary to resect a portion of the hyoid bone to insure complete removal and minimize possibility of recurrence

THYROID*

Thyroiditis

Acute thyroiditis seldom leads to suppuration and rarely requires surgical drainage or biopsy It is easily recognizable and responds to nonoperative treatment including irradiation therapy in small doses and antibiotics The chronic, firm, nonpainful strumas of Riedel's or Hashimoto's type must be differentiated from acute thyroiditis and from carcinoma Removal of the anterior portions of the thyroid gland and the isthmus is indicated for these strumas This operation forestalls contracture about the trachea, establishes histologic proof of the nature of the lesion, and leads to improvement in the general condition of the patient

* See also Chapter 29

sulting from chronic empyema or neglected hemothorax may cause contraction of the chest wall and the lung Formerly primary treatment was directed toward the infection, open drainage and when necessary secondary thoracoplasty being used Now, however, decortication technics which permit removal of the thickened pleura and scar from the lung and the chest wall often accomplish re-expansion of the lung and improvement of movement of the chest wall

Patients with acute empyema may be treated by multiple aspirations or tidal irrigations (Hart) supplemented by antibiotic and chemotherapy Some however require open drainage and a few may subsequently require decortication

Tumors of the mediastinum may be benign or malignant Benign and certain malignant lesions can be removed surgically Biopsy of inoperable lesions may reveal lymphosarcoma or other radiosensitive tumors Bronchogenic carcinoma is being recognized with increasing frequency and is treated by lobectomy or pneumonectomy with increasing safety Other benign tumors of the lung and certain localized inflammatory processes are similarly attacked

Bronchiectasis with serious disability may require removal of one or several lobes of the lung Patients with lung abscess in an early stage may be treated by postural *drainage, this treatment being aided by* repeated bronchoscopic aspirations and by the use of antibiotics or chemotherapy This often effects complete healing Chronic abscesses may require drainage through the chest wall or lobectomy Abscesses associated with empyema require drainage of the empyema Often however, bronchopleural fistulae develop which require closure by staged plastic operations Early recognition of acute abscesses and prompt aggressive treatment diminishes the number of patients requiring late and difficult operations

Lymphatic System

ENLARGEMENT of lymph nodes most frequently occurs as a result of acute or chronic infection of the extremity or part drained by them Postauricular lymphadenopathy, for example usually follows infection of the scalp Neoplasms should be suspected when enlargement of lymph nodes is not explained by infection or when lymphadenopathy is generalized Biopsy is often indicated Although sections thus obtained frequently reveal simple hyperplasia, at other times they establish a diagnosis of Hodgkin's disease, lymphosarcoma, leukemia, tuberculosis, or metastasis from a primary neoplasm elsewhere

Elephantiasis can occur as a result of obstruction caused by damage to lymph glands When lymphedema is present efforts should be made to determine the cause of infection or damage Filariasis may have caused the damage in some patients Usually, however, the trouble is due to recurring common superficial or cutaneous infections Treatment consists of elimination of infection reduction of size usually follows enforced rest and elevation of the limb and use of elastic support Occasionally plastic procedures with excision of subcutaneous tissue and grafting of skin or fascia are required

generally agree that discrete solid breast tumors should be removed and that facilities should be available for immediate histologic diagnosis by frozen section technics and for prompt radical mastectomy if the lesion proves malignant

Heart and Pericardium

EXPERIMENTAL surgery is enlarging the field of intracardiac operations on heart valves veins, and arterial anastomoses about the heart and is permitting attempts at improving collateral circulation for coronary obstruction However in spite of great interest and activity there is yet little agreement on indications for operation, technics or results Accordingly these newer developments will not be discussed in this chapter Instead more commonly practiced and available surgery will be outlined

INJURIES

Cardiac injuries caused by penetrating wounds in the heart may produce bleeding in the pericardial space and interference with proper filling of the heart (cardiac tamponade) Usually relief can be accomplished by aspirating the blood from the pericardial sac using a needle Occasionally persistent bleeding may necessitate emergency exploration of the pericardial space and repair of lacerations for control of hemorrhage

PERICARDITIS

Acute suppurative pericarditis may require repeated aspirations or, rarely, open drainage of the pericardium Great care must be taken to avoid secondary infection Chronic pericarditis particularly tuberculosis may effect thickening and contracture of the pericardium and partial or complete obliteration of the pericardial sac Cardiac embarrassment may lead to chronic failure with edema and ascites Extensive pericardectomy is an accepted operation Improvement of ascites particularly necessitates careful release of scar tissue around the inferior vena cava (Holmans)

TETRALOGY OF FALLOT

Tetralogy of Fallot the congenital deformity responsible for many of the 'blue babies can now be treated with gratifying results by the method of Blalock or the more recent method of Potts

Thorax, Pleural Cavity, Mediastinum, and Lung

THE thoracic cage may be deformed by congenital processes injury or long standing infection Depression of the sternum (cobbler s chest) is a typical example of a congenital deformity Embarrassment of the heart may occur from displacement or pressure and elevation of the sternum by surgery may be necessary Multiple fractures of the ribs may lead to paradoxical movement of the chest wall and respiratory embarrassment Relief can be obtained by elevating and fixing the loose segments of the ribs

Extensive thickening of the pleura re-

43. Secondary Shock

ROBERT C HARDIN

ALL physicians are faced from time to time with the problem of treating secondary shock The situation is always one of emergency and the doctor must act quickly and surely to prevent a fatal outcome Mistakes are commonly made in both diagnosis and treatment Shock may go unrecognized by those unacquainted with the clinical entities of which it is a part Treatment may be inadequate because the degree of blood volume depletion is inaccurately assessed Certain laboratory precedures will demonstrate both but are often unavailable or too time consuming The clinician must substitute judgment based on an understanding of the underlying mechanisms which produce shock and, in most cases, will find this adequate

DEFINITION

The definition of secondary shock cannot be expressed in a simple manner Shock is not truly an entity but appears as a part of many diseases or injuries The one constant characteristic encountered in all cases is loss of circulating blood volume Formerly, shock has been attributed to many causes but it appears now that these physiologic disturbances are simply a part of the clinical picture The work of Blalock and other investigators has shown that reduction of blood volume is the primary cause Tissue anoxia, sludging of blood acidosis and lowered metabolism result from this reduction

Depletion of Blood Volume

IT MAY seem almost too elementary to point out that blood volume may be depleted by loss of whole blood or of any of its constituent parts but this realization is a fundamental prerequisite for proper therapy The mechanism responsible for lowered blood volume is rarely the loss of whole blood plasma water, or formed elements alone Clinically these are most often encountered in combination with one predominating

The depletion may be sudden or require several hours Occasionally it is insidious particularly when the formed elements are diminished, and in this case there is compensation for the lowered blood volume until further insult occurs resulting in a rapid loss of a relatively small volume of

42. SURGICAL PRINCIPLES

Autonomic Nervous System

THE autonomic nervous system is frequently described in the older literature as the vegetative nervous system It provides the sole innervation of thoracic and abdominal viscera Many of the branches of its two main divisions, the sympathetic and the parasympathetic, are surgically accessible As understanding of the functions of these nerves increases and as knowledge of the etiology of diseases of organs or structures supplied by these nerves improves, surgical procedures directed toward the autonomic nervous system increase in number, vagotomy for peptic ulcer is an example of the use of operations on the parasympathetic division

Treatment of hypertension of the so called essential variety is an excellent example of the use of sympathectomy and is discussed in Chapter 15 The author prefers near total sympathectomy to splanchnicectomy because of greater and longer lasting improvement

Pain pathways visceral afferents, travel in the sympathetic nervous system Pain of recurring pancreatitis can be alleviated by splanchnicectomy (Smithwick) or celiac ganglionectomy (the author) as described elsewhere in this chapter Celiac ganglionectomy has also relieved pain from certain disorders of undetermined etiology such as biliary dyskinesia Stellate and upper thoracic ganglionectomy will relieve pain of angina although operation probably is rarely indicated The same procedure can be employed for certain forms of tachycardia since the effect of sympathetic heart denervation in man as demonstrated by near total sympathectomy is bradycardia

a fairly constant level This, however, represents but half the total blood volume The remainder is composed principally of erythrocytes Diminution of the *number of* red blood cells reduces the blood volume correspondingly without reduction in plasma volume except in profound anemia In severe anemia, such as results from chronic bleeding, the total blood volume may be reduced appreciably Shock does not result because the reduction takes place so slowly that adjustment of the organism is good Shock may ensue if there is a sudden loss of a relatively small part of the remaining blood volume added to this already considerable deficiency

OTHER MECHANISMS INVOLVED IN *THE PRODUCTION OF SHOCK*

For many years the question has been debated whether secondary shock results from simple blood volume loss or whether an upset humoral mechanism or some toxic substance released from damaged tissue might be the initiating factor As in many other such problems, it now appears that both answers are in part correct In most cases, injury or disease sets the stage for local loss of blood plasma It has been *adequately demonstrated,* however, that certain products of tissue autolysis and bacterial toxins arising in ischemic or infected tissues may produce shock In some instances this may be the initiating factor but usually is an additive one Theoretically, at least, shock so produced is at first primary with loss of vascular tonus and rapidly becomes secondary because of extravasation of plasma through damaged vessel walls Since such noxious materials reach every part of the body, the blood volume loss is not confined to the damaged area Several substances have been suggested as the toxin resulting from tissue breakdown *Further evidence is necessary, however, to* prove conclusively the identity or identities of the causative agent in each instance of shock following tissue damage Bacterial toxins have also been thought capable of acting in this manner and one, that of *Clostridium welchii,* has been incriminated beyond doubt

Symptoms

THE clinical appearance of the patient in shock is affected in some degree by the underlying *process* but *certain* signs usually may be observed The patient is pale and breathes shallowly He is usually apathetic but may be extremely apprehensive The skin is cold and clammy, *the superficial veins are* collapsed, and the pulse is weak and thready Recognition of these signs should initiate examination of the state of the circulation They are not in themselves pathognomonic of the existence of shock but may arise from other cause A critical evaluation is necessary to determine whether such signs depict blood volume diminution

STATE OF THE CIRCULATION

The first effect of lowered blood volume is a fall in venous pressure which diminishes the return of blood to the heart This in turn results in lowered cardiac output and arterial hypotension Low arterial *pressure is the most constant* sign of secondary shock and its presence in a patient suffering from some disease or injury commonly complicated by shock must never be disregarded *Lowered arterial systolic* pressure in such circumstances not only indicates diminished blood volume but may be used as a clinical measure of the degree of loss

the remaining blood In a person with chronic, severe anemia shock may attend a small hemorrhage The type of blood volume depletion depends on the underlying disease or injury, but the state of shock, once produced, is the same in every case Clinical perspective depends on an understanding of what part and how much of the blood volume may be lost under given conditions

LOSS OF WHOLE BLOOD

The most spectacular and most easily understood mechanism of whole blood loss is frank hemorrhage Depletion to shock levels may occur in a few minutes by bleeding externally into the gastrointestinal tract or into one of the body cavities There also may be significant loss of whole blood into damaged muscles in cases of long bone fracture Another common, and sometimes overlooked cause of blood loss is a surgical procedure That all these mechanisms may produce sufficient depletion of blood volume to result in shock has been amply demonstrated

LOSS OF WATER

Shock produced by dehydration alone is rarely encountered for to produce a sufficiently lowered blood volume the water loss must be both great and rapid In slowly developing dehydration the blood volume is not greatly altered because of a compensatory shift of fluid from the extravascular compartments Approximately 6 per cent of the body weight may be lost before dehydration becomes clinically apparent, yet if it has occurred slowly the blood volume is not diminished significantly The importance of dehydration in relation to shock lies in the fact that it is present in some degree in all cases This does not result from the loss of blood volume itself but reflects the patient's state of water balance before the appearance of shock or his inability or failure to drink after the acute incident responsible for the shock

There are, however, certain special circumstances under which shock from water loss alone may occur Severe vomiting or diarrhea, especially in children, are examples In these cases there is also loss of electrolytes with a concomitant acidosis or alkalosis Dehydration and electrolyte imbalance with production of shock are also an integral part of some endocrine and metabolic disorders

LOSS OF PLASMA

Loss of plasma occurs when there is injury to vessel walls without break in continuity or when there is obstruction of venous return Although other processes afford better illustrations the commonly accepted example of shock from this cause is found in cases of burn, when plasma escapes into the damaged tissues and from the surface of the burned area Plasma loss from venous obstruction is seen in intestinal lesions with embarrassment of the return circulation by compression or thrombosis This often happens in strangulated hernia, intussusception, volvulus, or intrinsic tumor The more rarely encountered entities of which plasma loss is a part include injury of vessels and tissues by prolonged interruption of arterial flow This may follow the tight application of a tourniquet, bleeding into a vascular sheath with compression of a major vessel, or crush injury In these instances, and particularly in the last, there may be complications attending the absorption of toxic products of tissue breakdown Shock from plasma loss is also seen in other cases of tissue destruction such as bile peritonitis and pancreatitis It may also accompany blast injury of the lung

LOSS OF THE FORMED ELEMENTS

The mechanisms which guard blood volume maintain the quantity of plasma at

anism, developing after loss of blood volume but having the peculiar attribute that its intensity may vary from one vascular bed to another Some vital organ may thereby be deprived of its blood supply *There is considerable evidence that such a* phenomenon may damage the kidneys Another peculiarity of vasoconstriction is that overcompensation, apparent by the production of a mild hypertension, may result Compensation is maintained until the blood volume is reduced 30 to 40 per cent Failure of the mechanism may then be gradual or abrupt Abrupt failure is often precipitated by some minor episode such as moving the patient

Complications of Shock

IT IS difficult to draw a line dividing the physiologic changes which are a part of shock from alterations in the functional capacity of individual organs which might be classified as complications of the condition No structure seems to escape completely and some may be permanently damaged All too frequently death results *from the resulting incapacity of some* organ

KIDNEY*

It has already been stated that renal damage may occur during shock Profound changes in blood flow through the kidneys resulting from oligemia have been demonstrated These consist of a reduction in volume flow and increased arterial resistance The consequence is reduced plasma clearance and oliguria In most cases the process may be reversed by treatment, but in some, even with adequate replacement of blood volume, the condition may progress to uremia

Just what part of renal damage derives *from* impaired circulation and how much arises from absorption of toxic agents from injured tissues is unknown There also may be intravascular hemolysis of incompatible blood used in treatment to add to the confusion It has been suggested that kidney failure may result from a summation of all these and that lower nephron damage of some degree always follows shock In any event, the possibility of irreparable renal disease always should be kept in mind Early and adequate replacement of blood *volume offers the best chance of prevention*

* See also Chapter 18

OTHER COMPLICATIONS

Often the first organ to be affected by anoxia incident to shock is the brain resulting in sudden respiratory failure The heart is also affected and cardiac failure is a frequent concomitant or sequela of shock An apparent myocardial depression following prolonged hypotension may explain why *the circulation of the shocked* person is sometimes easily overloaded Pulmonary edema has been noted during the first week following shock Whether this results from primary pulmonary damage or from left ventricular failure is unknown Liver function is profoundly deranged during shock and carbohydrate metabolism is altered There is failure of glycogen storage and poor absorption of dextrose from the gas*trointestinal tract*

Immediate Effects of Circulatory Failure

The effects of lowered blood volume and blood pressure are exerted on the entire organism—no part or function escapes. Several physiologic changes follow so closely that they are in reality a part of the clinical picture. Among these is anoxemia. The oxygen content of venous blood is sharply reduced. In the past, anoxia has been regarded as the cause of shock, however, it has been demonstrated recently that the maintenance of high arterial and venous oxygen tensions in the face of depleted blood volume does not alter the course of shock. Anoxemia must be regarded, therefore, as an effect of shock. Nevertheless, resultant damage to tissues cannot be disregarded. It is entirely probable that this mechanism is important in the development of irreparable tissue damage.

SLUDGING OF BLOOD

Another striking feature of oligemic shock is the redistribution of the formed elements of the blood, with the erythrocytes becoming trapped in the capillary beds. The blood in these vessels then has a higher hematocrit value than that in other parts of the vascular system. This blood remains in the periphery of the circulation and effectively reduces the circulating volume. Tissues normally supplied by the capillary beds so affected are deprived of their usual volume of blood flow. The appearance and severity of peripheral hemoconcentration parallel the fall in mean arterial pressure, and the phenomenon appears to be an effect of shock.

ACIDOSIS

Acidosis accompanies shock in greater or lesser degree. A diminution of the alkali reserve develops slowly and is proportional to the fall of arterial systolic pressure. This has been attributed to faulty tissue metabolism secondary to anoxia, with the accumulation of nonvolatile organic acids. However, administration of oxygen to the extent that normal saturations in arterial and venous blood are maintained does not prevent acidosis.

REDUCTION OF METABOLISM

Total oxygen consumption of the organism is reduced in shock. This phenomenon parallels the reduction in cardiac output. Although consumption may be maintained at normal rates by the administration of oxygen under pressure, the course of shock due to hemorrhage is not affected.

Compensatory Mechanisms

THE ability of the human body to withstand rather large losses of blood volume is repeatedly demonstrated. The blood donor is routinely bled of 500 cc without experiencing untoward results. Minor accidents, childbirth and surgical procedures may be attended by similar losses without apparent shock. Certain mechanisms exist which allow compensation for considerable diminution of blood volume. The most effective of these is vasoconstriction, which reduces the volume of the vascular space to be filled. Other mechanisms are tachycardia, which does not greatly increase the cardiac output, and hemodilution, which ordinarily increases the blood volume too slowly to be significant.

Vasoconstriction is not only the first line of defense against blood volume loss but is the only important compensatory mech

Although hemorrhage is the rule in traumatic shock, certain injuries are also characterized by loss of plasma from the circulating blood volume One of these is abdominal injury which does not rupture a solid organ or tear a large vessel but produces obstruction of the venous return from the bowel by thrombosis or some other mechanism The result is an outpouring of plasma into the lumen of the gut which may reach sufficient proportion to produce shock although the condition may not become apparent for some hours after the injury Plasma loss is also encountered in crush injury which may occlude a major artery to an extremity This is seen in victims of accidents who become pinned under fallen earth beams or masonry When the occlusion deprives tissues of their normal blood supply for a sufficient period they undergo degeneration After the pressure is released plasma escapes from the damaged vessels in the extremity and the patient may enter into a state of shock In these cases there is also hemorrhage but the essential loss is of plasma

BURN SHOCK

The usually cited example of shock from loss of plasma is that caused by burn injuries Depending on the severity of the burn and its extent varying amounts of plasma are exuded into the damaged tissue and lost from its surface This has been demonstrated to be the mechanism whereby depletion of blood volume arises It is important to realize however that burn shock is never the result of simple loss of plasma volume Early usually within the first twenty four hours a deficiency in erythrocytes develops This results from destruction of cells which apparently occurs in the peripheral circulation Third degree burn produces a greater depletion of cells than those of less severity Shock complicating burns must therefore be regarded as due to loss of both plasma and red blood cells

SURGICAL SHOCK

Shock developing during surgical procedures follows depletion of blood volume arising from a combination of factors Dehydration and plasma loss play some part but the important mechanism is whole blood loss As would be expected extensive surgical procedures are more apt to be attended by significant hemorrhage Thoracic operations particularly pneumonectomy and neurosurgery are often accompanied by considerable blood loss and abdominal surgery may be similarly complicated The possibility of blood loss exists during any surgical procedure even the simplest and the appearance of shock should be taken as evidence of dangerous blood volume depletion

OBSTETRIC SHOCK

Obstetric shock is due to hemorrhage Postpartum bleeding is the most common complication of delivery Other accidents encountered in pregnancy such as ectopic pregnancy and placenta previa may result in hemorrhage of sufficient degree to produce shock

TOXIC SHOCK

Certain toxins produce secondary shock These substances act like histamine First there is dilatation of the vascular bed (primary shock) and second there is loss of plasma from the dilated vessels Tissue breakdown products and bacterial toxins have been shown to possess the same attributes The sudden appearance of shock in patients with infected wounds or badly mangled extremities must be explained on this basis

SHOCK IN INTESTINAL OBSTRUCTION

Disease processes in the bowel which interfere with venous return from a segment result in pouring of plasma into the lumen Shock produced in this manner develops

Irreversible Shock

THE patient with shock which remains untreated will eventually enter a phase in which his life may no longer be saved by restoration of the circulating blood volume The exact mechanism whereby irreversibil ity arises is unknown Time is clearly established as a factor and in man de pending somewhat on accompanying injury and the severity of oligemia this period is from six to eight hours Death occurs from a variety of causes such as continued escape of plasma, renal failure, pulmonary edem myocardial insufficiency, or respirato failure Any of these may result fron changes already described It has also been suggested that an upset balance of the hormonal control of blood pressure may play a part There is no reason to believe, at present, that any one mechanism causes irreversibility At present, treatment in this stage is hopeless

Types of Shock

PHYSICIANS have come to link with the general state of secondary shock the names of several clinical entities in which it is commonly encountered This practice is in a sense incorrect, since there are no funda mental differences between the cases so classified The terms however are well established and allow rapid association be tween the fact of blood volume depletion and the reason for this fact The nature of the disease or injury responsible determines what portion of the blood is lost and knowledge of that fact is the basis of ra ional therapy

OUND SHOCK

Accurate measurement of plasma and cell lumes in patients with gunshot wounds s established that the depletion of blood ume results from hemorrhage There be concomitant dehydration but this ot ordinarily of significance Two ex ons to this rule are (1) wounds of the in which there is usually considerable l loss accompanied by shock which e out of proportion to its degree and (2) abdominal wounds where the hemor rhage may cause the initial shock Disturb ances in the circulation of the bowel may appear later and result in plasma loss Characteristically this occurs several days after wounding

TRAUMATIC SHOCK

Shock follows so many injuries that any generalization must be inaccurate Yet per haps the most constant feature of injury is hemorrhage the usual cause of accompany ing shock Stab wounds and incised wounds may sever blood vessels and cause rapid and considerable loss of blood Rupture of pa renchymatous organs may result in bleed ing of similar magnitude Crushing injuries of the chest or of an extremity are likewise characterized by hemorrhage Fractures, particularly if compound are commonly accompanied by bleeding sufficient to pro duce shock In fact injuries of extremities produce greater blood loss than those in any other region Second in this respect is abdominal trauma and third is injury of the chest

TABLE 62 BLOOD CONSTITUENTS LOST IN SHOCK

Type of shock	*Predominant loss*
Wound shock	Blood
Traumatic shock	Blood
Burn shock	Plasma and erythrocytes
Surgical shock	Blood
Obstetric shock	Blood
Shock in intestinal obstruction	Plasma
Medical shock	
Gastrointestinal hemorrhage	Blood
Dehydration	Water and electrolytes
Metabolic and endocrine disorders	Water and electrolytes
Acute infections	Water electrolytes and plasma
Tissue destruction	Plasma

plasma volume is usually higher than normal but coincident with the onset of peripheral circulatory collapse it becomes significantly lowered Shock usually results, however from some more spectacular disturbance Peritonitis or infection in muscle masses may give rise to bacterial toxins with sudden production of severe circulatory collapse Hemorrhage into the adrenal gland (Waterhouse Friderichsen syndrome)* may complicate many of the acute infectious diseases and produce shock through acute adrenal insufficiency

SHOCK IN TISSUE DESTRUCTION

Shock in tissue destruction results from exudation of plasma from a damaged part or serous surface Freezing, tissue autolysis bile peritonitis, and acute pancreatitis—as well as pulmonary damage caused by a lung irritant or blast injury—are recognized as entities which may be complicated by sufficient loss of plasma to be attended by shock

* See also Chapter 30

SUMMARY

In no type of shock is there depletion of one portion of the blood alone Dehydration, for example accompanies every instance of shock When plasma is lost into an injured extremity there is also some hemorrhage However, the underlying disease or injury determines the predominant loss from the blood volume These are recapitulated in Table 62

Diagnosis and Clinical Evaluation

THE recognition of shock ordinarily is not difficult if the possibility of its occurrence is kept in mind The diagnosis actually rests on determination that blood volume is depleted, which is done clinically by inference rather than by direct measurement After recognition there remains the necessity of discovering the type of blood volume loss and assessing its degree

RECOGNITION OF REDUCED BLOOD VOLUME

The symptoms and signs previously outlined are the usual occurrence in cases of shock However, these are not peculiar to that disorder and when unsupported by other evidence, they do not allow a definite diagnosis Furthermore certain patients may have extreme but asymptomatic hypo

slowly and may be overlooked by the physician Specific disturbances which may lead to such an occurrence are volvulus, intussusception, venous thrombosis, strangulated hernia, enteritis, and intrinsic tumors of the bowel Extrinsic tumors are not likely to interfere with circulation Products of tissue autolysis resulting from impaired circulation and toxins engendered by growth of bacteria in the lumen of the bowel may also under proper circumstances affect the course of shock in patients with intestinal lesions The patient is protected from their action so long as they are contained within the bowel Should perforation occur however, absorption through the peritoneum is rapid and toxic shock of the most profound degree quickly ensues In fact when an intestinal lesion is known to be present the abrupt onset of shock should be taken as evidence of perforation

MEDICAL SHOCK

The term medical shock is an ambiguous one which has come into usage as a more or less convenient heading under which to classify several unrelated processes Originally it meant shock not encountered in surgical patients With the restriction of the term surgical shock to cases of blood loss during operation the expression medical shock acquired broader connotation and no longer excluded shock in surgical patients It perhaps should be divided into at least four subgroups—shock in gastrointestinal hemorrhage shock in dehydration, shock in metabolic and endocrine disorders and shock in acute infections

Shock in Gastrointestinal Hemorrhage

This condition results from the reduction of blood volume by loss of whole blood The mechanism is directly apparent and requires no discussion The common lesions so complicated are peptic ulcer, esophageal varix, and malignant tumor

Shock in Dehydration

Shock in dehydration is not commonly encountered for there is rarely sufficient diminution of blood volume To produce significant oligemia, water loss must have occurred very rapidly (so that the circulating volume was not augmented from other compartments) or must be profound with great reduction of total body water Acute water loss of sufficient degree to produce shock sometimes accompanies vomiting or diarrhea, particularly in children There is always a concomitant electrolyte imbalance with acidosis or alkalosis Depletion of total body water occurs either from excessive but relatively slow, loss or from inadequate intake In hot environments sweating may account for a diminution of body fluids of 1000 cc per hour If this is accompanied by restricted intake and persons so exposed do not voluntarily drink sufficiently a considerable deficit may develop in a relatively short time Hypotension often follows which may be corrected in as short a period as thirty minutes by drinking of water

Shock in Metabolic and Endocrine Disorders

This type of medical shock is the result of dehydration augmented or initiated by electrolyte imbalance Diabetic acidosis perhaps furnishes the best example since it is characterized by a reduction of both cations and anions and a serious diminution of total body water Shock is a prominent feature in the complex picture of this profound disturbance Addison's disease is also marked by depletion of body water and of sodium chloride In a crisis, the plasma volume may be reduced 30 to 45 per cent with resultant shock and all its attendant physiologic disorder

Shock in Acute Infection

Shock may arise from a variety of causes in acute infection In lobar pneumonia the

Water Loss

Measurement of water loss by clinical means is extremely unreliable If the loss either has been large enough or has occurred quickly enough, anhydremia may result The hematocrit may be taken as an indication of the degree of blood volume *depletion but does not reflect* loss from the intracellular and interstitial compartment In chronic water and electrolyte loss all compartments are depleted When clinical signs of dehydration appear, the deficit of water may be assumed to be 6 per cent of the body weight

Treatment

THE *treatment of secondary shock involves* replacement of the kind and amount of fluid lost from the blood Estimation of the quality and quantity of depletion cannot be relied on for absolute accuracy, but may be used as a starting point Any plan of therapy will require revision according to the response of the patient This demands constant attention and frequent re evaluation

CHOICE OF FLUIDS AND ROUTES OF ADMINISTRATION

It is evident that three fluids will make up the bulk of replacement therapy—whole blood, plasma, and isotonic solution of sodium chloride Water by mouth also has an important, often overlooked, role The nature of the blood volume depletion will determine which fluid is used in treatment *Although replacement will be ac*complished largely with one, many cases will require all three In every instance, particular *attention should be paid to the* requirement for water because there is always some degree of dehydration

Water

Administration of water may be accomplished orally, rectally, or parenterally If the patient can cooperate and there is no contraindication to its ingestion, water is best given by mouth It makes little difference in what *form it is offered* except that *alcoholic beverages are* absolutely forbidden because of resultant vasodilatation Considerable augmentation of blood volume can be accomplished by oral administration or rectal injection of water, although the process is slow In simple water deprivation, drinking will quickly bring the patient to normal and no other form of treatment may be necessary In other cases where there is also much salt depletion the intravenous or subcutaneous injection of saline solution is the procedure of choice

Plasma

Plasma must be administered intravenously Effective replacement of blood volume is obtained with either isotonic or hypertonic plasma or albumin (human) solution The hypertonic preparations attract water into the vascular bed until a *normal concentration is achieved* This requires a supply of readily available water in the tissues which may not be found in *severe dehydration* Hypertonic protein solutions possess no advantage over normal plasma

Whole Blood

Whole blood, like plasma, must be injected intravenously It is the most useful fluid in the treatment of *shock because* it possesses the widest application When loss of whole blood has been great, replacement with whole blood is mandatory The use of

tension. The converse is also true when there is overcompensation with some of the symptoms of shock but a mild hypertension If rigid definition is insisted upon these cases may be regarded as representative of the two extremes of compensation rather than as examples of established shock Such lack of clear cut delineation is, however, characteristic of clinical problems The experienced physician will not be disturbed greatly by the failure of any process to conform to the usual

Two aids to diagnosis exist which are available at all times The first and most important is the nature of the underlying disease or trauma If it is such that lowered blood volume may be expected the meaning of symptoms and signs possibly due to shock becomes apparent Reference to the above discussion of the clinical types of shock and the accompanying table will make this more clear The second useful aid is measurement of the blood pressure When hypotension the most common sign of diminished blood volume is discovered in cases where shock might be expected the diagnosis may be considered established

DETERMINATION OF THE TYPE OF BLOOD VOLUME LOSS

After the loss of blood volume is determined the next point to be established is e part of the blood that has been lost ain the underlying process will serve as accurate guide Considerable aid may btained from the laboratory by simple atocrit determination erythrocyte or hemoglobin measurement * Hecentration of considerable degree is eristic in those instances where or water has been lost This may be by a pre-existing anemia Hemor in the long run compensated by ion but this is a slow process uring several days In such cases

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the hematocrit is normal or insig lowered for the first few hours Aga existing anemia may be reflected in hematocrit reading

ASSESSING THE MAGNITUDE OF BLOOD VOLUME LOSS

When the presence and nature of blood volume loss are determined, the magnitude of the deficit remains to be established In external bleeding, the volume of the hemorrhage may be fairly accurately estimated by observation In other cases of hemorrhage the blood pressure affords the most reliable indication of the amount lost Escape of 500 cc of blood from the vascular bed produces a fall of 10 to 20 mm Hg in systolic arterial pressure. This, of course, is masked by vasoconstriction unless the depletion is too great to be compensated. The point at which hypotension develops varies considerably but a blood volume diminished by 30 per cent is ordinarily reflected in lowered blood pressure A systolic arterial pressure of 100 mm Hg indicates a whole blood loss of less than 25 per cent and a systolic pressure of less than 85 mm Hg accompanies losses in excess of 25 per cent of the blood volume

Plasma Loss

Plasma volume depletion causes a measurable rise in the hematocrit, erythrocyte count and hemoglobin concentration proportional to the magnitude of the loss There are several formulae for calculating the volume of the missing plasma One of the simplest and most readily applied is that of Harkins In this method, each point of elevation of the hematocrit above 45 is taken to indicate a plasma volume depletion of 100 cc The same investigator has formulated a quick method of calculating the plasma deficit in cases of burn A depletion of 50 cc is assumed for eac cent of body surface involv

dle and gravity alone. Replacement may be attained faster by simultaneous administration into two veins or by some system of increasing pressure within the apparatus If the latter technic is employed precaution against air embolism must be taken

INTRA-ARTERIAL TRANSFUSION

Blood or plasma may be injected intraarterially A needle is inserted into the radial or femoral artery with the point toward the heart. A cannula has also been used with placement in a smaller vessel (dorsalis pedis) Blood is then administered under controlled pressure The pressure is maintained at 50 mm Hg until flow ceases, is then raised to 70 mm, and then by increments until a pressure of 100 mm Hg is reached The whole procedure requires but a few minutes Several advantages are claimed for this method (1) relief of myocardial ischemia by perfusion of the coronary vessels, (2) rapid restoration of the blood volume determined by actual capacity of the vascular tree and (3) restoration of breathing in the apneic patient This route of administration has proved useful in instances of massive hemorrhage It is also employed during cardiac and thoracic surgery when blood loss may be sudden and enormous The apparatus is assembled and arterial puncture done prior to beginning the operation If hemorrhage occurs it may be compensated quickly and accurately

FAILURE OF THERAPY

A patient's failure to respond to blood volume replacement may be because the shock has progressed into the irreversible state More frequently, however, it is due to some remediable factor The most common of these is continued loss of blood or plasma and diligent search for such loss should be made in all cases responding unsatisfactorily Another cause is absorption of *toxins (bacterial and autolytic)* from damaged tissues or the contaminated peritoneum

SPECIAL CONSIDERATIONS IN BURNS*

It is generally agreed that plasma should be used as the initial treatment of shock in cases of burn Formulas for calculating the dosage have been given The question of when and in what amount whole blood should be used in burns is perhaps the most difficult one in the entire field of shock That some is necessary to correct the deficiency resulting from destruction of erythrocytes is quite apparent Because anemia occurs within the first forty-eight hours and because plasma loss continues for at least seventy two hours the hematocrit level does not indicate the state of the blood volume after the initial treatment has been given There is no way, except actual measurement of the total blood volume, by which the exact nature of any deficit may be determined The clinician must depend on the knowledge that *destruction of erythrocytes always occurs* and on assessment of the state of the circulation

Administration of one or two pints of blood within the first twenty four hours and a similar amount during the second day seems indicated The state of circulation the blood pressure and evidence of hemoconcentration may be used to guide further therapy with plasma Burn shock has been successfully combatted by whole blood alone with results better than those obtained by use of plasma exclusively The indication would seem to be to use whole blood freely and in preference to plasma if any doubt exists as to the exact deficit of the circulating blood volume The most *important adjunct measure in treatment of* burn shock is an adequate water intake preferably by mouth but supplemented intravenously if necessary This should be

* *See also Chapter 4°*

xcessive plasma may result in profound nemia and anoxemia of dangerous degree n addition, when the cell volume is greatly epleted whole blood is the best agent for ffecting a permanent increase of total lood volume The enormous amounts of lood required in some cases, particularly hose in which surgical treatment must fol ow resuscitation raise the question of how nuch plasma may be used—if any Experi nce demonstrates that substitution of less han 1000 cc of blood by plasma is allow ble The use of plasma or human albumin olution in hemorrhagic shock is an emer ency or supplementary measure and will e found unsatisfactory as the sole method f replacement therapy

Choice of Vein

Any vein of sufficient size to permit clean ntry of the needle and insertion for a suffi ient distance to insure adequate fixation nay be employed Most transfusions are iven into the antecubital veins or into hose of the ankle Veins of the wrist and and as well as those of the scalp particu arly in infants, may be employed success ully The femoral vein may be entered with a long (2½") needle attached to a syringe The needle is inserted medial to the femoral artery just below the inguinal igament at an angle of 60° with the skin and in a plane parallel to the artery The insertion is made slowly until the vein is entered In a case of injury the vein chosen should be removed as far as possible from the probable site of debridement or other surgical procedure so that transfusion may be continued during other forms of therapy

Amount of Replacement

Assessment of the magnitude of the blood volume loss serves to indicate the amount of replacement necessary A fur ther guide is the progress of the patient In loss of whole blood transfusion of 500 cc may be expected to raise the systolic arterial pressure 10 to 20 mm Hg In severe hemorrhage the initial dose of blood will range between 1250 and 2500 cc Frequent re evaluation of the patient is necessary since blood loss may be continuous during transfusion, particularly in traumatic shock As much as 50 per cent of the transfused blood may be so lost in such cases If sur gical treatment must follow resuscitation further allowance for blood loss should be made Depending on the magnitude of the procedure, blood loss during operation may be as much as two or three liters Vol ume replacement of plasma may be judged on the same basis as that of blood with further guidance being furnished by fall in hematocrit value

Rate of Flow

The rate of flow of either blood or plasma is an important consideration since speed of replacement is a factor in prevent ing irreversible shock In severe cases the first 1000 cc should be given in thirty minutes and the first half of this may be given in five minutes The rate of flow of further infusions will be determined by clinical judgment but 20–40 cc per minute is not excessive When the systolic pressure is raised to 100 mm Hg the rate of flow should be slowed to 5 or 10 cc per minute Later when the patient seems to have stabilized this may be reduced still further or the transfusion stopped If surgical treatment is necessary a slow drip should be maintained until the patient has recov ered from anesthesia If need arises the rate of flow then may be increased to com pensate for blood loss encountered during therapy

The problem of injecting large amounts of blood or plasma intravenously in short periods may be met in many ways One of the factors limiting rate of flow which may be altered by the transfusionist is the size of the needle Rates of 40–50 cc. per minute may be obtained by use of a 16 gauge nee

thoracic and cranial injuries or in cases of respiratory distress Oxygen may be administered and is of great value when there is pulmonary disease or injury It is of no value in the treatment of shock itself since tissue anoxia is the result of circulatory failure, which is not corrected by this means *

After shock has been overcome and necessary definitive treatment accomplished the physician must watch for signs of the late complications of shock These include oliguria shortness of breath, and venous distention During convalescence, the patient should have a sufficient caloric intake with 70–100 Gm protein daily, 5–7 Gm sodium chloride per day and liberal amounts of water Intravenous administration of fluid should be avoided

*See Chapter 44

large enough to insure a urinary output of 50 to 100 cc per hour

SURGERY ON PATIENTS IN SHOCK

In many instances surgical treatment will follow restoration of the circulation Operation in such cases should be delayed if possible until the objectives of the primary therapy have been attained In some instances however continued blood volume loss will necessitate earlier institution of surgical procedures In those special cases where perforation of the gut or the presence of badly mangled or infected muscle masses have resulted in failure of treatment the surgeon faces a difficult decision At this point, clinical judgment may dictate repair of the perforation amputation of an extremity, or other suitable procedure as a possible life saving measure in the face of very grave risk

COMPLICATIONS OF TREATMENT

The complications of the treatment of patients in shock are those associated with blood transfusion The most important are pyrogenic reactions intravascular hemolysis and circulatory overload Pyrogenic reactions fortunately are not usually severe but the unstable state of the circulation renders a sharp rise in body temperature highly undesirable A fall in blood pressure with attendant deterioration of the circulation may ensue In event of such reaction the infusion should be stopped immediately and the fluid or blood together with the set being used for its administration discarded Intravascular hemolysis of incompatible blood during shock is of grave import Kidney damage already present may be augmented and a fall of blood pressure always occurs The transfusion should be stopped immediately and another of compatible blood started Both pyrogenic and hemolytic reactions may be minimized by careful attention to preparation of fluids and sets and by meticulous crossmatching of blood By far the most common sequela of the treatment of shock is circulatory overload As noted above, the circulation of the patient in shock is often easily hindered perhaps because of myocardial depression The physician must be watchful for signs of venous engorgement and pulmonary edema

AIDS IN TREATMENT

Although the prime consideration in the treatment of shock is qualitative and quantitative restoration of the blood volume many simple measures can hasten recovery or help prevent progression Among these aids are those aimed at making the patient comfortable Fatigue and pain should be relieved Careful attention to placement in bed with adequate support of injured extremities may do much to relieve pain and promote rest Fractures of long bones should be immobilized with sand bags or by other procedures not only to relieve pain but also because movement of the fragments may result in considerable hemorrhage

Judicious use of morphine or similar drugs is of great value, but overdosage must be avoided It may arise because during shock subcutaneously injected morphine may not be absorbed which may lead to repeated injections Absorption of all of the morphine then occurs when the circulation is restored This may be prevented by attention to total dosage and time intervals of injection or by the use of the intravenous route for the first administration Fifteen to thirty milligrams of morphine will usually relieve pain

In the past the patient in shock has been wrapped in blankets and heat applied externally This may induce sweating and result in loss of water and electrolytes The patient should be kept comfortably warm but should not be overheated Elevation of the foot of the bed (shock position) has some value but is contraindicated in

mechanism, therefore, may become acute emergencies

DYSPNEA

Respiratory action ordinarily occurs with little or no conscious effort In certain disease conditions the patient becomes aware of difficulty or increased effort in breathing, which he describes as shortness of breath, and for which we use the term dyspnea Objective measurements aid in evaluating the degree of dyspnea and the severity of the disorder of the respiratory mechanism The *vital capacity*, the maximum amount of air which the patient can breathe, is usually between 4000 and 5000 cc The *tidal volume*, the amount of air which is breathed under conditions of normal respiration is usually 500 cc per breath

Dyspnea may be caused by obstruction to the respiration by reduction of the tidal volume, or by a reduction of the vital capacity The closer the vital capacity approaches to the tidal volume, the greater is the sensation of dyspnea

Causes of Dyspnea

The basic causes of dyspnea may be divided into several categories There may be direct stimulation of the respiratory center or reflex stimulation from the carotid body due to anoxia Reflex stimulation of the respiratory center may be initiated by painful somatic impulses or by cerebral influences of an emotional character There may also be a sensitive Hering Breuer reflex causing early inhibition of inspiration, and, therefore a rapid shallow respiration

Failure of Respiratory Mechanism

Dyspnea is often a prominent feature in diseases involving the respiratory mechanisms the muscles of respiration, the respiratory passages and the lungs themselves Interference with the action of the diaphragm the intercostals, and the accessory muscles of respiration results in inadequate attempts at inhalation If the respiratory muscles function normally, an adequate amount of oxygen may not reach the alveoli because of reduced oxygen concentration in the inspired air, or there may be obstruction of the respiration due to disease of the nasal passages, mouth, pharynx, larynx trachea, or bronchi The exchange of gases between the alveoli and the blood may be diminished by abnormal conditions of the lung tissue itself, as in pneumonia, atelectasis, emphysema, and pulmonary edema An increased need for gas exchange is caused by any condition which produces an increase in metabolism, such as exercise, fever, and thyrotoxicosis

Neurogenic Dyspnea Diseases of the nervous system may produce dyspnea Examples of these are organic diseases such as encephalitis, intracranial tumor, and cerebral edema or hemorrhage, and functional conditions such as neurasthenia hysteria, and emotional disturbances

Circulatory Failure Dyspnea may be caused by a circulatory condition that interferes with the transport of respiratory gases such as shock, congestive failure or anemia It may also be caused by acidosis due to reduced alkali reserve or excess carbon dioxide

Cardiac Dyspnea Cardiac dyspnea may be caused by such conditions as pulmonary engorgement, pulmonary edema, and reduced elasticity and distensibility of the lungs These result in inadequate ventilation with carbon dioxide retention and arterial hypoxia Occurring usually at night cardiac asthma is an acute attack of dyspnea in patients with heart disease Although the cause of the attack is unknown, the symptoms are probably due to pulmonary congestion and a sudden decrease in the distensibility of the lung The tendency to pulmonary edema often results in a reduction of the oxygen saturation of the blood In patients with congestive heart

44. Anesthetic and Inhalation Therapy

JAY J JACOBY

TO PROVIDE relief from pain during surgical procedures was the first function of anesthesiology but its scope has been widened in recent years The skills acquired in producing regional anesthesia for surgery have been extended in the performance of diagnostic and therapeutic nerve blocks With increasing use these blocks are found to be of value in a continually increasing number of disease conditions The field of resuscitation is also included in anesthesiology because of the frequent occurrence of circulatory and respiratory difficulties in patients who are undergoing surgical procedures Skill in resuscitation so gained is applicable to emergencies which frequently occur outside the operating room and the hospital Anesthesiology encompasses a knowledge of the physiology of respiration and experience in the treatment of acute disturbances of respiratory activity and therefore includes inhalation therapy The mechanical features of inhalation therapy the handling of gases under high pressure and the operation of apparatus for the control of gas flow also make this field naturally suited to anesthesiology

Research in this specialty has the aim not only of improving anesthetic procedures for patients during operation but also of contributing to the store of knowledge in physiology and pharmacology and so to improve patient care

Inhalation Therapy

THE respiratory system provides oxygen and removes carbon dioxide If there is a disturbance in either aspect of respiratory function the existence of the organism is threatened The organism however is somewhat better able to withstand the retention of carbon dioxide than it is the deprivation of oxygen A factor of basic importance is that the body is unable to store oxygen Interference with the supply of oxygen for only a few minutes may result in death Disorders of the respiratory

respiratory center cause inhibition of inspiration, when the lung is deflated impulses from the lung cause exhalation to stop and inhalation to begin Ordinarily, the first portion of this reflex is the only one which functions

Anoxia Anoxia is not a stimulant to the respiratory center, rather it causes depression of this area of the brain Anoxia does, however, cause reflex stimulation of the respiration by acting upon the aortic and carotid bodies These chemoreceptors, located in the wall of the aorta and at the bifurcation of the carotid artery, are stimulated by lack of oxygen They are resistant to anoxia and retain their ability to initiate impulses for a long period of time When the respiratory center is depressed respiration is controlled by the chemoreceptor mechanisms The carotid and aortic bodies do not function under ordinary circumstances, but they act as the last protection against anoxic death because they maintain the respiration when all other mechanisms of control have failed

GAS CONTENT OF THE BLOOD

The concentration of nitrogen differs little in inhaled and exhaled air remaining about 79 per cent Inhaled air contains about 21 per cent oxygen and 0 03 per cent carbon dioxide exhaled air contains approximately 16 per cent oxygen and 4 per cent carbon dioxide

Normal blood contains about 15 *Gm* of hemoglobin per 100 cc The amount of oxygen with which 1 Gm of hemoglobin can combine is 1 34 cc 1 cc of oxygen is taken up by 0 75 Gm of hemoglobin When fully saturated arterial blood contains approximately 20 cc of oxygen per 100 cc (20 volumes per cent) Ordinarily, arterial blood is only 95 per cent saturated, and contains 19 cc of oxygen per 100 cc of blood In addition to the oxygen which is chemically combined with hemoglobin a small quantity (0 24 volumes per cent) is present in physical solution in the plasma

Carbon dioxide is present in the blood mainly in the form of bicarbonate, although a small amount is present in other chemical combinations and in physical solution Arterial blood normally contains from 40-60 cc of carbon dioxide per 100 cc of blood

Venous blood differs from arterial blood in having a higher content of carbon dioxide and a lower content of oxygen When arterial blood passes through the capillaries oxyhemoglobin separates into reduced hemoglobin and oxygen The oxygen diffuses through the capillary walls into the tissues Ordinarily, about 6–7 cc of oxygen are utilized from each 100 cc of blood Venous blood, therefore, returns to the lungs carrying 12–13 volumes per cent of oxygen During activity, the amount of oxygen utilized by the tissues is increased This is provided by an increase in the rate of respiration and in the rate of blood flow and also by an increase in the amount of oxygen removed from each cubic centimeter of blood

As the blood passes through the capillaries, carbon dioxide diffuses into it from the tissues The amount of carbon dioxide passing from the tissues into the capillaries is 6 cc per 100 cc of blood The ratio of oxygen removed from, and carbon dioxide added to the blood varies with the respiratory quotient

CYANOSIS

Cyanosis is the term used to describe the color of the skin, mucous membranes tissues, and blood when an excess of reduced hemoglobin is present in the blood Oxyhemoglobin has a bright red color reduced hemoglobin is much darker in appearance For cyanosis to be discernible there must be 5 Gm of reduced hemoglobin per 100 cc of blood The pigment of the skin and the condition of the circulation modify

failure difficulty in breathing is more pronounced when the recumbent position is assumed When an erect position is resumed the difficulty in breathing is diminished because the respiratory muscles have a greater freedom of movement and because blood drains from the chest and pulmonary congestion is relieved

CONTROL OF RESPIRATION

The respiratory center is a term applied to a group of nerve cells in the brain stem Impulses from these cells to the muscles of respiration cause breathing to occur An increase in the rate or depth of respiration called hyperpnea may be produced by an increase in carbon dioxide concentration or by any other factors which serve to modify the respiratory pattern Apnea the condition in which there are no attempts to breathe and all respiratory movement ceases can be produced by decreasing the carbon dioxide tension either through voluntary or artificial hyperventilation or through depression of the respiratory center by disease or drugs

Chemical Control of Respiration

Under ordinary circumstances the control of respiration depends upon chemical stimulation of the respiratory center with carbon dioxide acting as the principal stimulant The center may also be stimulated by acids reduction of the blood supply or change in the *p*H of the blood Small alterations of these factors will produce a pronounced change in the respiratory pattern

Cheyne-Stokes Respiration

Periodic breathing (Cheyne-Stokes respiration) is caused by an abnormality of the respiratory center with decreased sensitivity resulting in weak and shallow respiration or momentary cessation of respiration During this period the concentration of carbon dioxide in the blood stream increases until the depressed respiratory center is again actively stimulated and respiration increases in rate and depth The accumulated carbon dioxide is now removed by increased pulmonary ventilation and respiratory movement again becomes shallow In a typical case of Cheyne-Stokes breathing respiration is shallow and slow it gradually increases in rate and depth until the pulmonary ventilation is greater than normal and then subsides into its previous depressed state Periods of apnea may occur

Voluntary Control of Respiration

Usually without conscious effort the movements of respiration are integrated with other activities of the organism In speaking and laughing there is considerable modification of respiration and swallowing and coughing cause a temporary inhibition of respiration The ability to inhibit respiration voluntarily is present for only a short period of time usually about sixty seconds or less Following this period of breath holding the involuntary mechanisms of respiration cause contraction of respiratory muscles Emotional influences may decidedly alter the rate and rhythm of respiration Fear suspense anxiety and excitement all modify the respiratory pattern

Reflex Control of Respiration

The stimulation of almost any afferent nerve may influence the respiratory movement in a reflex manner Coughing sneezing and the inhibition of respiration which follows the inhalation of an irritating gas are examples of modification of respiration due to afferent impulses Stimulation of muscles joints or viscera and painful stimuli from any part of the body modify the respiratory pattern

Hering Breuer Reflex The Hering Breuer reflex is important in controlling respiration It has two parts when the lung is inflated impulses from the lung to the

Stagnant anoxia may be general as in heart failure or shock or it may be local as in obstruction of the circulation to a part of the body Local stagnant anoxia may appear in such conditions as embolism thrombosis or injury of a vessel or when the part is exposed to cold

Histotoxic Anoxia

Histotoxic anoxia occurs when the tissues are unable to utilize the oxygen supplied to them as in cyanide poisoning Although a normal amount of oxygen is present in the blood the ability of the cells to perform the functions of metabolism is decreased and the consumption of oxygen by the cells is reduced

Symptoms of Anoxia

The symptoms of anoxia depend on the degree of severity of the condition *Mild anoxia* produces psychic changes such as impaired judgment and over confidence and headaches are frequently present. The respiration may show a slight increase in rate and depth The blood pressure may remain normal but the pulse rate usually increases *Moderate anoxia* produces impairment of vision dizziness anxiety and nausea and vomiting The rate and depth of respiration is increased and the patient is aware of air hunger The blood pressure shows a sharp rise the pulse may become irregular and then slow Muscular movements become incoordinated followed by twitching and spasms *Severe anoxia* causes weakness delirium and coma Respiration becomes depressed both in rate and depth and finally stops The blood pressure falls and the pulse becomes imperceptible Convulsions followed by muscular relaxation may occur In the terminal stage of severe anoxia the pupils dilate and become fixed and centered resembling pupils seen in deep anesthesia The presence of cyanosis depends on the hemoglobin concentration the pigmentation of the skin and the state of the peripheral circulation

The reduction of oxygen tension at high altitudes may cause anoxia in airplane pilots without their being aware of the condition Because the early signs of anoxia include impaired judgment and vision it is likely that a number of airplane accidents are due to unrecognized anoxia in pilots who fly at high altitudes without supplemental oxygen inhalation

HYPERCARBIA

Inadequate elimination of carbon dioxide may result from conditions interfering with the transmission of gases across the alveolar membrane or with the free exchange of air between the alveoli and the atmosphere The retention of carbon dioxide therefore frequently occurs in association with anoxic anoxia When there is carbon dioxide retention alone the condition is called hypercarbia if there is associated anoxia the condition is called asphyxia

An excess of carbon dioxide in the blood stream may lead to psychic manifestations resembling those caused by anoxia Respiration increases in rate and depth and the pulse and blood pressure may increase There may be twitching and spasm of muscle groups followed by convulsions If carbon dioxide excess becomes severe the respiration pulse and blood pressure become depressed The color of skin and mucous membranes is usually good because of peripheral vasodilatation but if anoxia of sufficient degree is superimposed the patient may become cyanotic

ADMINISTRATION OF OXYGEN

Inhalation therapy is administered to help in the treatment of disease conditions associated with general or localized anoxia If oxygen is administered and the oxygen tension of the alveolar air is increased a greater quantity of oxygen enters the blood in the pulmonary capillaries The inhalation of 100 per cent oxygen results in an increased quantity of physically dissolved oxygen as well as in an increase in the oxy

the appearance of cyanosis Ability to identify cyanosis varies greatly even with trained observers

Significance of Cyanosis

The significance of cyanosis varies with the amount of hemoglobin in the patient's blood The lower the hemoglobin level the more ominous is the significance of cyanosis For example a normal individual showing slight cyanosis would have 10 Gm of oxyhemoglobin and 5 Gm of reduced hemoglobin per 100 cc of blood This patient is not in grave danger An anemic person who has 8 Gm of hemoglobin would have only 3 Gm of oxyhemoglobin if slight cyanosis were present This quantity of oxyhemoglobin is barely sufficient to maintain oxygenation of the vital centers An exceptionally anemic patient who has only 5 Gm of hemoglobin may die of anoxia and yet never have a sufficient amount of reduced hemoglobin to produce cyanosis In contrast patients with polycythemia may have a somewhat cyanotic appearance with a normal amount of oxyhemoglobin Such a patient might have 13 Gm of oxyhemoglobin plus 5 Gm of reduced hemoglobin

ANOXIA

Anoxia or more properly hypoxia is the term applied to any condition in which the tissues fail to receive an adequate supply of oxygen Factors to be considered are the oxygen saturation of the blood the total quantity of hemoglobin the circulation of the blood and the ability of the tissues to utilize the oxygen supplied to them On this basis anoxia is divided into four types anoxic anemic stagnant and histotoxic These conditions may occur independently or in combination

In anoxic anoxia the oxygen saturation of the blood is reduced In anemic anoxia the amount of available hemoglobin is reduced In stagnant anoxia the speed of the circulation is reduced In histotoxic anoxia the ability of the tissues to utilize oxygen is reduced

Anoxic Anoxia

Anoxic anoxia may be caused by a decrease in the oxygen tension of the inspired air such as occurs at high altitudes or when the inspired air is diluted with other gases It may be caused by interference with the passage of air into the lungs due to obstruction of the respiratory passages or paralysis of the respiratory muscles It may also be caused by diseases of the lung such as pneumonia emphysema atelectasis and pulmonary edema or by the surgical removal of lung tissue Extrinsic diseases involving the lung such as pneumothorax or hydrothorax may also cause anoxic anoxia by reducing the ability of the lung to perform its function Severe pain with respiration as in pleurisy and rib fractures may be responsible for a decrease in respiratory amplitude capable of producing anoxic anoxia Congenital disease of the heart which allows mixing of venous and arterial blood may also produce anoxic anoxia

Anemic Anoxia

Anemic anoxia occurs in any condition in which the hemoglobin concentration is greatly reduced with chronic anemia and acute hemorrhage being the most common causes Chemicals which combine with hemoglobin and render it nonfunctional also produce anemic anoxia Carbon monoxide nitrite and chlorate poisoning are the most common examples of this form of anemic anoxia In these states an adequate amount of hemoglobin may be present but it is chemically combined and unable to act in an oxygen-carrying capacity

Stagnant Anoxia

Stagnant anoxia occurs when the circulation is depressed to such an extent that the supply of oxygen to the tissues is reduced

serted through the nostril far enough so that its tip is just beyond the level of the soft palate and is visible in the oropharynx This length is about the distance between the edge of the nose and the tragus

If the patient swallows oxygen the catheter should be withdrawn until the swallowing has ceased The catheter should be removed and cleaned every eight hours and it should then be re inserted into the other nostril Attention to cleanliness, lubrication humidification and changing of the catheter will result in minimal irritation of the nose and throat

The concentration of oxygen that the patient receives by the nasopharyngeal catheter method of administration may be roughly calculated as follows For each liter per minute the concentration rises 3 to 4 per cent To obtain a concentration of 50 per cent oxygen the rate of flow should be about 8 liters per minute ($8 \times 4 = 32 + 21 = 53$) For a small patient this may be obtained with 1 liter per minute less and for a large patient 1 additional liter per minute should be administered

Oxygen Masks Oxygen may be administered by the mask method in concentrations up to 100 per cent Two types of oxygen masks in common use are the B L B mask and the meter mask Each is obtainable in a nasal or oronasal type The oronasal mask covers the mouth and the nose, the nasal type covers the nose only and leaves the patient's mouth free for speaking and for the ingestion of fluids and food

The *B L B mask* has two sponge rubber valves and there is a small breathing bag attached For the administration of 100 per cent oxygen the rate of flow should be so adjusted so that the breathing bag does not empty at the end of inspiration If less than 100 per cent of oxygen is desired the rate of flow of oxygen should be regulated so that the breathing bag is filled for only a part of the inspiratory phase During the remainder of inhalation, room air is admitted through the sponge rubber disks and this may produce a slight increase in resistance

The *meter mask* permits the administration of 100 per cent oxygen, and there is no resistance to breathing when lower concentrations are used If less than 100 per cent of oxygen is desired an attachment provides for calibration of the oxygen concentration by rotating a disk the concentration of oxygen can be accurately set from 40 per cent to 100 per cent The meter mask is also provided with a device for the administration of oxygen under positive pressure The orifice of the exhalation valve may be selectively narrowed so that exhalation occurs at a pressure of from 0–4 cm H_2O The availability of positive pressure is valuable and its use will be discussed later

Oxygen may be employed as the vehicle for carrying drugs into the lungs By using a nebulizer, bronchodilator and antibiotic drugs may be obtained in the form of a fog Inhalation of the mist brings the drugs into direct contact with the mucous membrane of the respiratory tract If a rubber tube from an oxygen tank is attached to the nebulizer instead of a hand bulb larger quantities of drugs can be administered A substantial amount of drug is exhaled and lost but if a mask and rebreathing bag are used as provided by an oxygen mask apparatus drug loss is diminished

A relatively new modification of the mask method of inhalation therapy is the *demand flow regulator* This apparatus is equipped with an ordinary rubber mask without a rebreathing bag It is attached to an oxygen cylinder which may be left open without the escape of oxygen When the mask is applied to the patient's face the oxygen begins to flow at the moment that inhalation begins The patient inhales 100 per cent oxygen during the entire inspiratory phase During exhalation the

gen saturation of the hemoglobin In a normal person there is an increase of over 2 cc of oxygen per 100 cc of arterial blood In persons suffering from anemic and stagnant anoxia the benefit of oxygen administration results from a similar increase in the blood oxygen In anoxic anoxia the administration of oxygen causes a substantial increase in the amount of oxygen combined with hemoglobin in addition to increasing the amount present in physical solution For this reason the most dramatic results of oxygen therapy are noted in the treatment of anoxic anoxia

Indications for Oxygen Therapy

Conditions in which oxygen therapy is frequently of value include diseases of the lungs heart and central nervous system as well as others Among disease of the *lungs* that benefit from oxygen administration are pneumonia atelectasis infarction edema asthma emphysema tuberculosis and injuries by direct trauma blast and irritant gases Diseases of the *heart* for which oxygen therapy is indicated include congestive failure coronary spasm coronary occlusion acute infectious processes and trauma Diseases of the *central nervous system* include cerebral vascular accidents and brain injuries *Miscellaneous conditions* in which oxygen is a valuable adjunct in therapy include shock hemorrhage asphyxia and respiratory obstruction depression and paralysis Oxygen administration is also of value in determining the viability of the bowel during laparotomy Administration of 100 per cent oxygen to the patient will cause the cyanotic bowel to regain its color rapidly if it is viable otherwise resection of the bowel is necessary

Methods of Administration

Common methods of oxygen administration are by mask nasal catheter and oxygen tent The value of oxygen therapy is more or less independent of the device used for administration Generally the effectiveness of oxygen therapy depends on the concentration of oxygen administered equal concentrations of oxygen administered by any means are of equal value The nasal catheter and mask methods of administration are relatively simple The equipment required is inexpensive and maintenance problems are minimal Initial cost of an oxygen tent is high maintenance of the equipment is more troublesome and considerably more care is needed in the administration of oxygen by this means Concentrations of oxygen that can be obtained by means of the oxygen tent and the nasal catheter are approximately the same about 60 per cent being the maximum With the mask method of administration concentrations of oxygen up to 100 per cent may be obtained

Nasopharyngeal Catheter The nasal catheter method of oxygen administration is the most simple Concentrations of oxygen from 25 to 60 per cent may be obtained depending upon the rate of flow of oxygen This method is particularly valuable for patients intolerant of the mask or the tent Irrational or delirious patients may be given oxygen with a minimal amount of disturbance

Certain precautions must be observed for efficient use of the nasal catheter Moisture should be added by means of a humidifier attached to the oxygen cylinder if this precaution is not observed there may be drying crusting and ulceration of the mucous membrane The catheter used should be of soft rubber with multiple perforations in the tip if oxygen is administered by means of an ordinary catheter through a single hole the stream of oxygen impinges on one area of the mucous membrane and causes irritation

Before inserting the nasal catheter the flow of oxygen should be started and the therapist should make certain that oxygen is emerging from the perforations in the catheter When properly lubricated with a water soluble lubricant the catheter is in

tion is of little or no value, although it has been recommended in the past Asphyxia indicates the presence of an oxygen deficit and an increased concentration of carbon dioxide in the blood stream The respiratory center is exposed to a concentration of carbon dioxide greater than normal The administration of carbon dioxide to increase the blood concentration still more is not logical Treatment of asphyxia should aim to increase the intake of oxygen, and for this reason 100 per cent oxygen should be employed

Atelectasis

Because of the increase in ventilation caused by the inhalation of carbon dioxide it is frequently used in the prevention and treatment of atelectasis Following abdominal operations there is a decided decrease in tidal volume and vital capacity, the respiratory excursions of the patient are reduced because of pain The increased depth of breathing caused by carbon dioxide inhalation results in improved expansion of the alveoli If atelectasis of mild degree is present the inhalation of carbon dioxide may be of value in treatment Too much reliance should not be placed upon carbon dioxide inhalation either in the prophylaxis or treatment of atelectasis because the presence of a mucus plug is probably the most important etiologic factor The treatment of atelectasis should be directed at eliminating the plug of mucus

are inadequate cleansing of the tracheobronchial tree should be performed either by bronchoscopy or by suction through an endotracheal tube

Hiccough

Inhalation of carbon dioxide is frequently effective in treating hiccough which is caused by increased activity of the phrenic nerve center, initiating th contractions of the diaphragm When car bon dioxide is administered, the respirator center is so stimulated that it again re sumes the control of respiration an abnormal activity of the phrenic center suppressed The control of hiccough i this manner may be temporary and it ma be necessary to repeat treatment at interval of several hours

Carbon Monoxide Poisoning*

In the treatment of carbon monoxid poisoning inhalation of carbogen (mix ture of 5–7 per cent carbon dioxide an oxygen) should be employed An increas in the concentration of carbon dioxide i the blood decreases the affinity of hemo globin for carbon monoxide The hig oxygen concentration is valuable in th correction of the anemic anoxia To in crease the amount of hemoglobin availabl for oxygen transport, transfusions of whol blood may also be needed in severe cases

Methods of Administration

The methods of administration of carbor dioxide therapy are relatively simple The procedure used by lay people is to have the patient breathe in and out of a paper bag Exhaled air contains 4 per cent carbon dioxide and the concentration of carbon dioxide in the paper bag rapidly increases Carbogen should be administered by the mask method similar to that employed for the inhalation of oxygen alone The gas should be allowed to flow into the breathing bag as the mask is placed upon the patient s face

An even simpler method of carbon dioxide therapy utilizes pure carbon dioxide A rubber hose attached to a cylinder of carbon dioxide is held a few inches above the patient s face The gas is allowed to run out of the tube at a rate of several liters per minute Since carbon dioxide is

*See also Chapter 50

flow of oxygen from the cylinder stops The negative pressure required to initiate the flow of oxygen is minimal This device has the advantage that the patient receives 100 per cent oxygen during inhalation and that there is no re breathing of gases *The demand flow regulator* is probably the most satisfactory method for the self administration of oxygen It is particularly valuable for cardiac patients who have intermittent cardiac pain They may have the mask at their bedside at all times with the oxygen cylinder open whenever oxygen is needed the patient places the mask upon his face Considerable psychic benefit is derived from the knowledge that oxygen is immediately available

Oxygen Tent The oxygen tent is probably the most comfortable and satisfactory method of oxygen administration for patients requiring prolonged oxygen therapy Not only does it provide an increased oxygen concentration from 25 per cent to 60 per cent but it also provides for cooling and conditioning the atmosphere Occasionally patients may dislike the oxygen tent because of claustrophobia although this is uncommon with the transparent canopy

The canopy must be secured firmly under the sheets and mattress to maintain a virtually airtight closure Examination of the patient and nursing care should be performed through the canopy openings which must be carefully sealed after use Each time the canopy is raised the tent should be flushed with oxygen to restore the oxygen concentration When beginning therapy and after each interruption the oxygen flow should be set at 15 liters per minute for fifteen minutes to raise the concentration of oxygen to 50 per cent

The maintenance flow of oxygen should be about 10 liters per minute The atmosphere inside the oxygen tent should be checked for temperature and analyzed for oxygen content several times daily It will frequently be found that the concentration of oxygen in the tent is lower than the physician desires and expects This may be caused by improper securing or too frequent opening of the canopy, or by an inadequate rate of flow of oxygen

Fire Hazard with Oxygen

Oxygen does not burn and is not explosive Oxygen-enriched atmospheres however, create a fire hazard because they allow combustion to proceed more rapidly and more intensely A lighted cigarette will burst into flame when exposed to a high oxygen concentration Similarly, an ordinarily innocuous spark from an electrical device may cause a fire

Smoking should be prohibited in the vicinity of oxygen cylinders and oxygen therapy equipment and electrical devices should not be permitted near a patient receiving oxygen If oxygen under high pressure comes into contact with flammable material an explosion may result because of rapid combustion Oxygen connections therefore should never be oiled or lubricated

Criteria for Discontinuing Oxygen Therapy

The administration of oxygen should not be discontinued suddenly When clinical appearance of the patient indicates that oxygen administration may no longer be necessary the concentration or rate of administration should be reduced The respiration appearance and color of the patient should be watched the pulse should be counted carefully and frequently A rising pulse is an indication that oxygen administration is still needed

CARBON DIOXIDE

Therapeutic use of carbon dioxide is based upon the fact that inhalation of this gas increases respiratory activity In treating asphyxia carbon dioxide administra

than the inhalation of 100 per cent oxygen This therapy may be a life saving measure in the treatment of status asthmaticus or obstruction of the respiratory tract

Pure helium should never be used because it does not support life helium should always be administered in a mixture with oxygen Cylinders containing 80 per cent helium and 20 per cent oxygen are readily obtainable The simplest method of administration is by the B L B or meter mask The technic of administration is the same as that used in administering 100 per cent oxygen If a concentration of oxygen greater than 20 per cent is desired additional oxygen may be added from another cylinder

ADMINISTRATION OF GASES UNDER PRESSURE

Obstructive dyspnea may occur during *the inspiratory or expiratory phase of* respiration In either case the patient uses greater muscular effort to accomplish the exchange of air The pulse rate rises and cardiac failure may occur particularly if there is pre existing disease of the heart Administration of oxygen or helium and *oxygen by the simple* mask technic will be of some value

If oxygen or helium oxygen mixtures—preferably the latter—are administered under positive pressure to patients with obstructive dyspnea the sucking action in the chest is diminished or counteracted Positive pressure during inhalation tends to force the gas beyond the obstruction reducing the muscular effort required by the patient In pulmonary edema the positive pressure *tends both to prevent further* exudation of fluid and to promote its reabsorption It should therefore be an important therapeutic measure in the treatment of pulmonary edema In the asthmatic, positive pressure during the inspiratory phase causes *inspiration to become* more rapid and allows a greater time for the occurrence of expiration Positive pressure during the expiratory phase tends to maintain greater patency of the lumen of the bronchi

Positive pressure respiration may be secured by the meter mask, the helmet hood or by the use of an anesthetic gas machine The *positive pressure helmet hood* consists of a transparent plastic hood fitting over the head and secured at the neck by a rubber collar The atmosphere within the hood is easily conditioned and controlled The helmet hood provides pressure during both phases of respiration the *meter mask* provides pressure during exhalation only An *anesthetic gas machine can be used to provide pressure during* both phases of respiration The pressures obtainable are easily regulated and oxygen or helium oxygen mixtures may be used.

Positive pressure may be intermittent the treatment lasting for one or two hours and repeated three or four times daily Oxygen therapy by the nasal catheter or *tent* method may be used between positive pressure treatments Additional forms of therapy should be used as indicated

The amount of pressure used is regulated by exhalation valves that should be set at *pressures of 2–5 cm H_2O although at times* slightly higher pressures may be useful If the amount of pressure is excessive it causes a decrease in the return flow of blood to the heart a diminished cardiac output and a fall in blood pressure Excessive pressures may damage the lung tissue

heavier than air it flows downward and the patient inhales an increased concentration of carbon dioxide It is important that pure carbon dioxide should never be administered by means of mask inhalation apparatus as the patient would be completely deprived of oxygen and subjected to a very toxic concentration of the gas The reducing valve and flowmeter used for pure carbon dioxide should never be used for oxygen or carbogen because pure carbon dioxide contains droplets of oil which deposit in the reducing valve If oxygen or carbogen at high pressure is then run into the apparatus an explosion may result For this reason, the equipment should be plainly marked for use with carbon dioxide only

The concentration of carbon dioxide and the duration of the therapy are determined by the effect produced The pulse should be taken before and during the treatment If the pulse rate increases by more than 20 beats per minute or becomes weak or irregular, therapy should be discontinued The patient should be carefully and constantly watched during the administration of carbon dioxide therapy in order to prevent overdosage The development of a pronounced hyperpnea indicates that the therapeutic effect of carbon dioxide has probably been achieved and that the administration should be discontinued No patient should be allowed to inhale carbon dioxide or carbogen for more than five to ten minutes

In the treatment of hiccough prolonged administration of carbon dioxide should not be employed If the treatment is unsuccessful the concentration of carbon dioxide should be increased Ten or even 15 per cent carbon dioxide may be administered for a period of one to two minutes until the patient experiences dizziness and clouding of consciousness It may be necessary to repeat the treatment several times before control of hiccough is obtained

Administration of carbon dioxide is contraindicated in patients having serious hypertension or cardiac disease and in those suffering from asphyxia or debilitated by severe illness

HELIUM

The therapeutic use of helium is based upon the fact that, with the exception of hydrogen helium is the lightest of all the elements It is not flammable and does not support combustion A mixture of 80 per cent helium and 20 per cent oxygen has a specific gravity one third that of air or oxygen A gas with a low specific gravity passes through a constricted orifice with greater velocity and at a lower pressure than a gas with a high specific gravity Consequently, mixtures of helium and oxygen are of value in the treatment of obstructive lesions of the respiratory tract

When obstruction to respiration exists the patient tends to compensate by using increased muscular effort During inspiration this increases the negative pressure in the chest This tends to increase the exudation of fluid from the capillaries into the alveoli and bronchi If prolonged obstruction to respiration occurs during the expiratory phase emphysema and bronchiectasis may occur When obstruction is present either in the inspiratory or expiratory phase or both anoxia may occur because of decreased pulmonary ventilation The increased effort of breathing when prolonged or severe may result in overwork of the heart and exhaustion

The commonly encountered obstructive diseases of the respiratory tract include bronchial asthma and stenosis of the larynx trachea or bronchi caused by edema inflammation trauma and tumors In these conditions helium and oxygen mixtures reduce the physical effort of breathing and increase the tidal volume For this reason the inhalation of helium and oxygen mixtures is of greater value

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If oxygen or helium oxygen mixtures—preferably the latter—are administered under positive pressure to patients with obstructive dyspnea the sucking action in the chest is diminished or counteracted Positive pressure during inhalation tends to force the gas beyond the obstruction reducing the muscular effort required by the patient In pulmonary edema the positive pressure tends both to prevent further exudation of fluid and to promote its reabsorption It should therefore be an important therapeutic measure in the treatment of pulmonary edema In the asthmatic, positive pressure during the inspiraotory phase causes inspiration to become more rapid and allows a greater time for the occurrence of expiration Positive pressure during the expiratory phase tends to maintain greater patency of the lumen of the bronchi

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Resuscitation

THE emergencies which threaten life are usually those affecting the respiratory and circulatory systems. The aim of resuscitation is to restore these systems to normal as quickly as possible. When needed, resuscitative measures should be applied promptly. In very serious cases a minute or two may make the difference between the life or death of a patient. In less severe conditions the prompt application of resuscitative measures may prevent the progress of the disturbance. Emergencies involving the circulatory system for which resuscitative measures are of value are hemorrhage, shock, and cardiac arrest. The respiratory emergencies are due to depression, obstruction, or arrest of respiration.

The symptoms and treatment of hemorrhage and shock are discussed in Chapter 43.

CARDIAC ARREST

Cardiac arrest may be due either to ventricular fibrillation or to cardiac standstill and it is the final cause of death in many conditions. If there is serious basic illness cardiac arrest may be irreversible; under certain circumstances, however, it may be amenable to treatment. Cardiac arrest may occur in otherwise normal persons as a result of lightning or electric shock, trauma, reflex responses to intense peripheral or emotional stimulation, and the administration of anesthetic drugs and epinephrine. In many instances, particularly in patients under anesthesia, anoxia due to respiratory difficulties is the principal cause of cardiac arrest.

When the heart stops the movement of blood ceases and oxygen is no longer transported to the tissues. Of all the organs in the body the brain is the most sensitive to the lack of oxygen. Cellular changes, often irreversible, occur in the brain tissue after five minutes of anoxia. Cerebral edema also occurs and contributes to the symptom complex. The patient may show symptoms of cerebral damage and then progress to more or less complete recovery. This is true when cerebral edema is present, rather than cellular destruction. Cerebral damage may cause death or leave permanent signs, consisting of personality changes, muscular incoordination, convulsions, decerebrate rigidity, or coma.

Cardiac arrest is an emergency requiring the greatest promptness in the application of resuscitative measures. To be truly successful in the treatment of cardiac arrest, resuscitation must be applied within five minutes after the arrest occurs, so that the blood supply of the brain is re-established during this critical period. Every physician and every surgical team should have a predetermined plan for the treatment of cardiac arrest.

Diagnosis. The diagnosis of cardiac arrest during surgery is usually made by the anesthetist, from the abrupt disappearance of the pulse and blood pressure, and associated cessation of respiration. The anesthetist then should request the surgeon to stop the operative procedure, and to palpate one of the large blood vessels available in the operative field. If the surgeon is unable to palpate a pulse in the aorta, the iliac vessels, the carotid, or the subclavian artery, the diagnosis of cardiac arrest is confirmed.

Treatment. The time of cardiac arrest should be noted and artificial respiration with oxygen should be started immediately. A long needle should be inserted into the heart through the fourth intercostal space adjacent to the sternum. If the stimulus of the needle puncture does not cause the heart to resume beating 0.5 cc. of 1:1000 epinephrine and 5 cc. of 1 per

cent procaine should be injected through the needle The epinephrine is administered to stimulate the heart, and the procaine to prevent ventricular fibrillation

This procedure should be completed within three minutes from the time of diagnosis During this time, assistants should obtain a scalpel and retractors If the heart does not begin to beat after the injection of epinephrine and procaine, manual artificial circulation—sometimes called cardiac massage—should be started

Cardiac Massage. This procedure provides an adequate blood supply to the vital organs during the time that the heart does not beat If cardiac arrest occurs during the course of an abdominal operation, the surgeon should incise the left side of the diaphragm Under other circumstances, a long incision spread by retractors should be made in the fifth left intercostal space The physician places his hand through the incision and around the heart, squeezing the heart and expelling the blood from its chambers An alternative procedure is for the surgeon to place his unoccupied hand over the sternum and to compress the heart against the chest wall The compression or squeezing should be performed in a rhythmic manner approximately sixty times per minute Filling of the heart takes place in the interval between compressions This maneuver should expel a sufficient amount of blood from the heart to create a palpable pulse and to supply the vital organs with oxygenated blood

When satisfactory artificial respiration and manual artificial circulation have been achieved efforts should be directed at initiating the return of the heart beat The heart may begin to beat spontaneously after a few minutes of rhythmic compression or following repeated injections of small amounts of epinephrine and procaine To diminish the likelihood of ventricular fibrillation during treatment a few cubic centimeters of 1 per cent procaine should be dropped on the pericardium every te minutes An intravenous infusion of 0 1 pe cent procaine in isotonic sodium chlorid solution or glucose solution should also b administered If ventricular fibrillation i present, or occurs during treatment, pre viously prepared electrodes should b placed on the heart and an electric shoc should be administered Defibrillation ma thereby be accomplished Restoration o the heart beat may occur after an hour o longer, cardiac resuscitation should be con tinued until postmortem changes appear

When cardiac rhythm is re established the lung should be inflated and the ches should be closed Artificial respiratio should be continued until the patien re-establishes efficient, spontaneous respira tory movement Oxygen therapy shoul be continued and the patient should b closely watched, as cardiac arrest may agai take place The patient should be kept a complete bed rest and all the equipmen necessary to reinstitute resuscitative meas ures should be kept at the bedside

RESPIRATORY EMERGENCIES

If depression or obstruction to respira tion continues anoxic injury to the mecha nisms that control respiration supervenes and efforts to breathe finally cease A knowledge of artificial respiration is essen tial in treatment in either case

Obstructive interference with respiration may occur in many conditions In patients undergoing surgery, obstruction to respiration may be caused by spasm of the masseter muscles during an excitement stage by relaxation of the tongue and the soft tissues of the pharynx, by laryngospasm by copious secretion of saliva and mucus or by foreign bodies and regurgitated material in the pharynx Tumors or inflammation of the respiratory passages may be a cause of respiratory obstruction Drowning is probably the most common cause of respiratory obstruction which occurs outside of

the hospital Aspiration of foreign bodies into the lower respiratory tract creates a serious type of respiratory obstruction In intoxicated individuals and patients under anesthesia pieces of food and regurgitated material may be aspirated Children may aspirate nuts, coins and other objects

Cessation of respiration may occur in patients with brain injury or disease following lightning or electric shock, or in patients who have been poisoned with depressing drugs Respiratory arrest may also occur in patients under anesthesia due to excessive doses of anesthetic agents or curare Involvement of the respiratory muscles in poliomyelitis may cause weakness or paralysis of respiratory movements

Treatment

The treatment for respiratory emergencies falls into two basic categories removal of the obstruction to respiration and restoration of adequate oxygen intake If a suction device is available foreign bodies and liquids may be aspirated from the respiratory passages If suction is not available obstructing material may be removed from the mouth and pharynx without mechanical assistance The patient should be placed in Trendelenburg position with the head turned to the side in this position gravity will help to prevent the aspiration of material into he larynx A finger should be inserted into he patient's mouth and the respiratory assages should be wiped clear of foreign aterial

A patent airway can usually be obtained extending the patient s head and sup rting his chin The head may be moved n side to side and various degrees of nsion may be tried to ascertain the t favorable position The physician ld stand behind the head of the pa because this position gives him the est mechanical advantage If extension head and support of the chin do not provide a patent airway, the physic should flex his index fingers and place the behind the patient s mandible The low jaw should then be moved anteriorly far as possible This maneuver frequentl brings the tongue out of its obstructing position Another satisfactory method o preventing obstruction by the tongue is to place the fingers under the patient s chin and the thumb upon his lower teeth and to pull the mandible forward A curved artificial airway may be inserted into the patient s mouth, or his tongue may be grasped with a piece of gauze or towel and pulled forward

A clear airway having been obtained *artificial respiration* may be performed by the rhythmic compression and release of the patient s chest This may be accomplished by intermittent pressure upon the patient s sternum and ribs The pressure should be moderate to avoid injury to the bony skeleton The physician should be able to feel and hear the passage of air into and out of the patient s respiratory tract by placing his ear over the patient s mouth The physician should remain at the head of the patient Compression of the chest may be delegated to an assistant

An effective means of artificial respiration is that of *mouth to mouth insufflation* With the patient s chin supported in the position described and the patient s mouth held slightly open the physician places his mouth closely over that of the patient and then blows into the patient s mouth The physician then moves his head slightly to the side and takes a breath the patient passively exhales at this time This maneuver is repeated about fifteen to twenty times a minute and with each insufflation the patient s chest should be seen to expand Insufflation should be coordinated with the physician s breathing so that the procedure may be continued at length without undue fatigue

The technique of artificial respiration

now recommended by the American Red Cross and the Council on Physical Medicine of the American Medical Association for use by the general public is the *back pressure–arm lift method* The patient is placed prone with the head turned to the side The arms are bent upward so that the patient s cheek rests upon his hands The operator kneels on one knee at the patient s head and places his other foot near the patient s elbow The operator s hands are placed over the patient s chest He puts pressure on the patient s chest by rocking forward until his arms are vertical He then rocks back and slides his hands to the patient s arms The patient s arms are pulled upward until resistance is felt The arms are then dropped The maneuver is repeated about twelve times a minute There is evidence that this technic creates greater air exchange than other methods of artificial respiration used by the general public

If *mechanical aids* are available for artificial respiration most of the standard resuscitators are satisfactory The resuscitator should be adjusted to provide oxygen under moderate degrees of positive pressure When positive pressure is excessive damage may occur to the patient s lungs The maximum safe positive pressure is 20 mm Hg For infants the pressure should not exceed 14 mm Hg Regardless of the type of resuscitator used a clear airway must be maintained Visible expansion of the patient s chest should occur with each cycle of the resuscitator Expansion of the chest is the most important criterion of satisfactory artificial respiration If artificial respiration is to be performed for a prolonged period the use of a respirator or iron lung is the preferred method

When artificial respiration may be needed for a prolonged period as in bulbar poliomyelitis or cerebral damage tracheotomy should be performed * Tracheotomy is recommended for the dual purpose of providing a clear airway and permitting the aspiration of secretions from the tracheobronchial tree

Artificial respiration may be satisfactorily accomplished by the use of an *anesthetic gas machine* The breathing bag of the gas machine should be filled with oxygen with the mask placed snugly over the patient s face The breathing bag is then intermittently compressed to force oxygen into the patient s lungs Moderate pressure should be used and maintenance of an adequate airway is a primary consideration With either an anesthetic gas machine or a mechanical resuscitator it does no good to apply oxygen under pressure if the oxygen does not have access to the patient s lungs because of obstruction of the respiratory passages

Every physician should be prepared to administer effective artificial respiration The methods of chest compression and mouth to mouth insufflation require no equipment and may be used in any emergency A simple device may be prepared by each physician and kept in his office or car so that he may administer artificial respiration with oxygen at any time The equipment consists of a face mask a breathing bag a length of rubber tubing an oxygen tank and appropriate connections

Tracheal Intubation The ability to pass a tube through the larynx and into the trachea may be a life saving one Mastery of this technic is probably the most important single thing the physician can learn about resuscitation in respiratory emergencies Intubation of the trachea eliminates upper respiratory obstruction and permits the performance of artificial respiration with the assurance that oxygen is entering the patient s lungs Intubation of the trachea also allows aspiration of foreign material from the trachea and bronchi Mucus blood or vomitus may be removed from the tracheobronchial

*See Chapter 36

tree if a suction catheter is passed through the endotracheal tube This accomplished the physician may administer effective artificial respiration with a minimum of effort. With an endotracheal tube in place, any of the methods of artificial respiration may be used successfully

The insertion of an endotracheal tube is a relatively simple procedure The physician can learn to intubate the trachea in a day or two of instruction from an anesthesiologist or a bronchoscopist Practice on a cadaver, before rigor mortis sets in will enable the physician to master the technic The patient is placed on his back with the head extended and a laryngoscope is inserted into the mouth The tongue and epiglottis are elevated and the larynx is brought into view A suction catheter or an endotracheal tube is then inserted between the vocal cords and into the trachea The endotracheal tube should not be long enough to enter a bronchus Severe anoxia in which artificial respiration is most important produces relaxation of the jaw muscles and facilitates visualization of the larynx

Resuscitation of the Newborn Infant The basic principles of oxygen therapy and resuscitation apply to the infant both before and after birth The fetus in utero may suffer from anoxia because of a partially separated placenta prolonged labor, sustained and intense uterine contractions trauma to the brain or numerous other conditions When fetal anoxia is suspected 100 per cent oxygen should be administered to the mother thereby increasing the oxygen content of the blood of the fetus

The mechanism whereby respiration is initiated in the newborn infant is not clearly understood Delay in the onset of respiration is probably caused by three principal factors anoxia of the fetus in utero trauma to the brain and depressing drugs administered to the mother Some causes of fetal anoxia have already been enumerated The sedatives, narcotics and general anesthetics administered to the mother also depress the fetus The greater the quantity of pain relieving drugs administered to the mother, the greater is the fetal depression The methods of regional anesthesia for the mother—spinal, caudal and nerve block—ordinarily do not depress the fetus

Immediately after birth suction should be employed to clear the infant s respiratory passages of amniotic fluid and debris If the infant does not begin to breathe spontaneously, an adequate airway should be established by extending the head and holding the chin and tongue forward The lungs should then be inflated by the use of a resuscitator or by mouth to-mouth breathing Excessive inflation pressure must be avoided because of the danger of producing trauma to the lung with resulting pneumothorax and pneumomediastinum Injection of stimulating drugs is of doubtful value Gentle physical stimulation, e g slapping the soles of the feet, rubbing the back, or dilating the rectal sphincter, may be useful *Violent physical punishment* of the infant should be avoided as it may be traumatic Intubation of the trachea cleansing of the tracheobronchial tree by suction and tracheal insufflation of oxygen should be performed if the infant does not respond quickly

If the infant is depressed and needs oxygen after breathing has started it should be placed in an oxygen incubator where the temperature humidity and oxygen concentration can be controlled Administration of oxygen by a funnel in an open crib is practically worthless

OVERDOSE OF DEPRESSING DRUGS*

When a patient is found at home or brought to the hospital in a comatose state many factors are to be considered in the differential diagnosis Some conditions that

* See also Chapters 22 and 50

are possible causes of coma are diabetic acidosis hyperinsulinism epilepsy shock uremia, or the moribund phase of any disease Involvement of the central nervous system may be a frequent cause of coma as in cerebral vascular accident meningitis encephalitis and brain tumor Among the poisons that characteristically produce depression and unconsciousness are overdoses of the barbiturates opiates ethyl alcohol chloral and carbon monoxide Progressive depression of the central nervous system produces an overpowering sleepiness and a deepening coma The respiration is depressed earlier and to a greater extent than is the circulation Respiration becomes shallow and may be inadequate for maintaining oxygenation so that cyanosis may supervene In carbon monoxide poisoning a scarlet or reddish brown color is often noted In morphine poisoning slowing of the respiration is more pronounced The reflexes are depressed and the body temperature frequently falls When the circulation is affected the pulse becomes weak and the blood pressure is lowered

Morphine Poisoning*

Delayed morphine poisoning may result from the therapeutic administration of morphine examples of this were noted during the last war Severe injuries shock and prolonged exposure to cold decrease the peripheral circulation subcutaneous injections of morphine are not absorbed into the general circulation If the patient complains of pain he may receive repeated doses of morphine Following successful treatment for shock the patient s peripheral circulation improves All the morphine previously administered now enters the general circulation at the same time and the patient soon develops morphine poisoning Following an injury patients frequently suffer more from anxiety than from pain and the presence of shock further decreases the need for narcotics In shock patients opiates should be administered intravenously so that they immediately enter the general circulation and very small doses should be used

*See also Chapter 43

Treatment

Treatment of the poisoned patient depends on the severity of the depression If respiration is satisfactory in depth and rate and the circulation is not depressed little need be done except to empty the stomach to prevent further absorption of drug The patient should be watched closely to be certain that his symptoms do not become more serious It is not necessary to restore consciousness by administering stimulants The patient should not be aroused and compelled to walk, because this may produce exhaustion

If the poisoning is moderately severe respiratory obstruction may occur because of relaxation of the jaw and tongue muscles A patent airway should be restored and oxygen administered Carbon dioxide and carbogen should not be used Relief of obstruction may so improve the respiration that the tidal volume becomes adequate and cyanosis disappears If the depression of respiration is severe the ventilation may remain inadequate because of slow or shallow breathing The physician should attempt to increase the intake of oxygen by the administration of respiratory stimulants or by mechanical artificial respiration The latter is a more reliable method than dependence on drug action A clear airway should be assured if necessary by the insertion of an endotracheal tube A resuscitator or an anesthetic gas machine should be used to administer oxygen with intermittent pressure For prolonged treatment a respirator should be used because its action more closely approaches the physiologic mechanisms of breathing Endotracheal tubes may be used for several days

but they should be changed and cleaned every twelve hours

Respiratory Stimulants For morphine poisoning nalline is a new antagonist nikethamide and caffeine sodium benzoate are satisfactory respiratory stimulants In barbiturate poisoning caffeine sodium ben zoate metrazol nikethamide ampheta mine or picrotoxin may be used sodium succinate may be of value These drugs should be administered intravenously To provide access to the vascular system it is wise to start an intravenous infusion drugs may be injected into the infusion tubing Following the first injection one fourth to one half the initial dose of the stimulant may be administered every five minutes until the desired effect is ob tained Picrotoxin may be given at a rate of 1 mg per minute Improvement of respira tion rather than restoration of consciousness should be regarded as the therapeutic ob jective

When the ventilation of the patient be comes adequate the frequency of drug ad ministration should be reduced Return of the corneal reflex indicates that an ade quate amount of drug has been admin istered If administration of stimulants is continued for the purpose of producing a return of consciousness there may be un desirable results The stimulants cause an increase in the oxygen demand of the tissues at a time when their ability to obtain oxy gen may be decreased Excessive doses of stimulants may produce twitching and con vulsions When a patient has been severely poisoned it may be necessary to administer treatment for several days The quantity of stimulating drugs used during this period may be enormous

Support of Circulation Support of the circulation in the moderately depressed pa tient may consist of the intravenous admin istration of 5 per cent dextrose in water at a moderately slow rate Excessive use of normal saline for intravenous administra tion is accompanied by the hazard of pro ducing edema The use of plasma should be restricted to those conditions in which it is specifically required If the patient has been severely poisoned and the circulation is greatly depressed administration of whole blood transfusions may be indicated If the patient s blood pressure falls below its normal level it may be restored to nor mal by adding a vasopressor drug to the intravenous infusion Neo-synephrine 5 mg or ephedrine 50 mg may be added to 1000 cc of 5 per cent dextrose in water The flask should be shaken to insure com plete mixing Within a few minutes after the administration of this solution is begun the patient s blood pressure rises The rate of infusion should be adjusted so that the patient s blood pressure is maintained at approximately its normal level The blood pressure may be increased or decreased by an appropriate change in the rate of ad ministration of the infusion

If signs of cardiac failure occur they should be treated by the intravenous ad ministration of a soluble digitalis product and rapid digitalization should be effected

Other important supportive measures include the maintenance of the body tem perature and the prevention of pulmonary complications The patient should be turned frequently from side to side and antibiotics should be administered Secre tions should be removed from the mouth and pharynx and not be allowed to ac cumulate If severe poisoning has occurred cleansing of the tracheobronchial tree through an endotracheal tube should be performed Bronchoscopy may be indicated for the prevention or treatment of atelec tasis

CONVULSIONS

Convulsions may be produced by over dosage of stimulants and by diseases involv ing the central nervous system Convulsive conditions include epilepsy brain tumor

trauma to or degeneration of the brain, anoxia or asphyxia tetanus, and severe infectious diseases in children Stimulating drugs may produce convulsions that have a characteristic appearance depending on the site of action of the drug Strychnine and caffeine produce symmetrical, tetanic convulsions because of stimulation of the spinal cord Clonic and asymmetrical medullary convulsions are produced by picrotoxin, camphor, and asphyxia Convulsions usually result from extreme stimulation of the motor centers When convulsions are caused by disease, treatment should be directed toward eliminating the basic disease process

If severe, convulsions cause a rise in blood pressure exhaustion and interference with the ability to breathe During a severe convulsive seizure muscle spasm interferes with the patient s respiration in two ways, respiratory obstruction may be produced, or the muscles of respiration may become so involved as to be unable to perform their function In either way, asphyxia supervenes

Treatment

Symptomatic treatment of convulsions sustains the life of the patient so that the basic disease may be overcome or the poisonous drug may be detoxified or excreted If the convulsions are infrequent and mild, the chief concern is to protect the patient from injury placing a prop between the teeth and padding under the head and extremities If convulsions are prolonged but moderate in severity and spontaneous respiratory activity is satisfactorily maintained oxygen should be administered by means of a tent If a nasal catheter or a mask is used the patient may be so stimulated as to increase the frequency duration, or severity of the convulsions

Sedation During severe convulsions the patient may become cyanotic and respirations may become inadequate for a prolonged period To decrease the spasm and to permit respiratory activity to be maintained, sedatives or anesthetics should be administered For convulsions of short duration probably the best treatment is the intravenous administration of soluble barbiturates, such as sodium pentothal sodium nembutal, and sodium amytal For more prolonged control of convulsions "avertin' by rectum may be preferred or sodium phenobarbital may be administered If 'avertin' is used, the directions for its preparation must be strictly followed. A dose of 50 to 60 mg per kg body weight is usually adequate to control convulsions If the barbiturates are used intravenously they should be administered slowly, in an amount just sufficient to reduce the muscular rigidity The administration of those drugs may be repeated at intervals of two to four hours as necessary The use of curare as an anticonvulsant, particularly in tetanus, is still experimental

In severe convulsive conditions pneumonia and atelectasis are frequent complications, developing because of inadequate respiratory activity and because of aspiration of secretions into the tracheobronchial tree Patients having convulsions often produce an excess of mucus and saliva or are unable to swallow their secretions, which should be removed frequently by a suction catheter It is important to prevent the aspiration of secretions into the tracheo *bronchial tree*

The physician should be prepared to prevent or treat complications that may result from the administration of sedatives Having stopped the convulsions the physician may find his patient unable to maintain an airway and the recommendations regarding treatment of patients with respiratory obstruction should be followed Large doses of stimulants frequently produce depression as their ultimate effect The sedative drugs used to control convul

sions may add to the depressing effect of the poison For this reason also the dose of sedative drugs should be kept at a minimum

During the course of a convulsive disorder if the respirations become inadequate to maintain life artificial respiration should be administered in a gentle manner

Regional Anesthesia

THE injection technics of the anesthesiologist are becoming increasingly useful in diagnosis and treatment Injections of local anesthetic drugs serve to block nerve impulses If the desired change occurs after the injection it is an indication that the disturbance probably has a neurogenic background Otherwise there is probably an organic change in the involved tissues Used as a method of therapy the injection of local anesthetic drugs improves abnormal neurogenic conditions or those caused by local tissue disturbances Local anesthetic drugs may be injected into the spinal canal where they affect the spinal nerve roots into or around large peripheral nerve trunks or they may be injected to interrupt the impulses of the small nerve filaments in the various tissues

LOCAL ANESTHETIC DRUGS

Injection procedures are usually performed with aqueous solutions of the common drugs such as procaine metycaine intracaine xylocaine pontocaine and nupercaine These drugs may also be used in oil solutions Among other drugs used in therapy are eucupin ammonium sulfate (sarapin) and alcohol These drugs are listed in the order of increasing duration of action Oil solutions and procaine in propylene glycol (efocaine) have a greater duration of action than aqueous solutions but their use is restricted to deep injections Of the local anesthetic drugs procaine is the least toxic the maximum dose of procaine is 1 Gm In equal doses pontocaine is ten times as toxic as procaine and nupercaine is twenty times as toxic as procaine The dosage of these drugs should be appropriately reduced Procaine is used in solutions of 0 5 or 2 per cent Pontocaine is used in a 0 1 per cent solution Nupercaine is used in a solution of 1 1500 or 1 2000 The more concentrated solutions of local anesthetic drugs may be used for nerve blocks for widespread infiltration the dilute solutions should be used

Hyaluronidase may be added to the local anesthetic solution Its effect is to increase the spreading of the solution and thereby to increase the proportion of successful injections

Toxicity

The toxicity of local anesthetics depends in part on the concentration used and in part on total dosage The greater the amount and the more concentrated the solution the more frequent is the incidence of toxic reactions True allergy to local anesthetic drugs rarely occurs Most local anesthetic reactions are caused by a rapid entry of the drug into the blood stream with a resulting high blood concentration and precautions should be taken to prevent this During infiltration protection against intravenous injection is provided by continually moving the needle the injection should be performed during the insertion and withdrawal of the needle When the injection is performed with the needle in one place as for nerve block the plunger

which is the principal complaint If trigger points and extreme tenderness on pressure are present the prognosis with this form of therapy is frequently good. Physiotherapy may be a very valuable adjunct and should be administered immediately following the injection treatment *

A complete history and physical exam ination should be performed to rule out basic serious diseases such as diabetes syph ilis and neoplasm The physical examina tion should include a careful measurement of disability and range of motion Trigger points should be sought and if found marked for later injection

A sterile syringe and a long 22 gauge needle should be used for the injection The preferred drug is 0 5 per cent procaine The area to be injected should be cleaned with soap and water followed by zephiran or alcohol A skin wheal should be raised over the area of greatest tenderness and through this the long needle should be in serted into the trigger point This will fre quently reproduce the most severe type of pain experienced by the patient The anes thetic solution should be injected while the needle is moved back and forth through the painful area

The patient is then instructed to move the extremity and attempt to reproduce the most severe pain Occasionally after the principal trigger points have been in jected the patient will find other points previously unnoticed of lesser pain These also should be injected The patient should then move the extremity through its full range of motion and he should particularly go through the movement which previously had been most painful

Following the injection physiotherapy may advantageously be employed One treatment may sometimes relieve the con dition Often however after the anesthetic effects of the procaine disappear the pa tient may for a short time complain of pain more severe than that which he had prior to the injection. The procedure may be re peated each day or at intervals of two or three days Following successive injections the intensity of recurrent pain diminishes Frequently three or four treatments provide complete relief

* See Chapter 45

Mechanism of Action The mechanism by which relief is accomplished in these in stances is difficult to explain The pharma cologic effect of procaine in the tissues is present for about an hour After the anes thetic effect disappears it might be ex pected that the tissues would return to their previous state of increased sensitivity to pain The commonly accepted explanation is that a vicious cycle is broken The origin of the pain is postulated to be a minor in jury of which the patient may have been unaware followed by muscle spasm caus ing increased pain and more muscle spasm The relief of pain for a short time by the injection of a local anesthetic, results in diminished muscle spasm This causes less pain and the cycle goes in a reverse direc tion so that a return to normalcy may be accomplished Another theory is that small fibrous bands and adhesions form in the tissues These adhesive bands are perforated by the multiple needle thrusts and are broken by the distension of tissues pro duced by the volume of anesthetic solution

Trauma

Direct trauma produces disability caused by pain muscle spasm and limitation of motion Roentgenograms should be taken when indicated to rule out the possibility of a fracture If no fracture is present im mediate local treatment by infiltration of anesthetic drugs may frequently prevent a period of prolonged and serious disability For example sprains of the ankle may be treated satisfactorily in this way

The physician should carefully palpate the painful areas to locate the most sensi tive point which should then be injected

The patient should be asked to walk If additional areas of pain appear at this time, the injection should be repeated until there is complete freedom from pain and until the ankle may be moved through its complete range of motion The patient should be instructed to walk and exercise the ankle preferably at his normal activity In many instances, disability is completely eliminated This treatment may also be used for the ankle if a small chip fracture is present If the patient is not seen early and there is considerable edema, the result will be less satisfactory

Fractures not requiring immobilization are often painful Injections of local anesthetic drugs into and around the fracture site will frequently provide a great deal of pain relief The fractures that may be handled in this manner include those of the ribs the transverse processes the fibula and the coccyx

Low Back Pain

Low back pain is one of the most annoying conditions the practitioner is called on to treat It is difficult to diagnose and the treatment is often unsatisfactory The physician should rule out the presence of serious underlying disease such as herniated nucleus pulposus arthritis metastatic malignant lesions of the spine and disease of the spinal cord itself as well as abnormalities of posture The physician should then attempt to treat the patient symptomatically Trigger points frequently may be elicited in the muscles and ligaments of the back and around the large joints Nodules may be encountered, representing small herniations of fat through the lumbodorsal fascia Strains of the great muscles of the back and thigh may also cause this pain Injections of the trigger points and painful areas as described above combined with physiotherapy yield satisfactory results in this condition

Superficial Lesions

Where the painful lesion is superficial, a spray of ethyl chloride may be substituted for the injection of a local anesthetic Ethyl chloride causes rapid cooling of the tissues which is moderately painful When the spray is discontinued, the involved area develops a reactive hyperemia and at times there is considerable pain relief The tube of ethyl chloride should be held at a distance of about one foot from the site of application and a stream of the liquid should be allowed to play on the involved area Treatment should last for only a few seconds because freezing of the tissues will result if it is used for a longer period Ethyl chloride is also a general anesthetic and the vapor should not be inhaled

Scar Tissue

Pain in scar tissue represents a difficult problem for both the physician and the surgeon This pain may occur in amputation stumps or in the scar of a surgical incision It may result from a neuroma or from pinching of a nerve in scar tissue The excision of an amputation neuroma will usually cure the condition Pain may return, however, after the neuroma has been excised If a neuroma cannot be demonstrated, or if pain returns after the neuroma has been excised infiltration of dilute anesthetic solutions into the involved area may be helpful A single injection may provide complete and permanent relief of a condition that has been present for months or years More often several injections may be required to accomplish this goal If the patient obtains complete relief from pain when the injection is performed and if the relief lasts for only about an hour the injections should be repeated on two or three occasions. If a similar result is obtained each time, the painful scar tissue should be excised This may be accomplished under the local anesthesia produced at the time of the last test injection In some instances a simple exci

sion of the scar will eliminate the patient's complaints

Abdominal Trauma

A severe blow over the abdomen often provides a serious diagnostic problem for both the internist and the surgeon. The patient may complain of severe abdominal pain following the blow. Physical examination will demonstrate boardlike rigidity of the abdomen and there is a tentative diagnosis of rupture of a viscus. However, laparotomy may fail to demonstrate a lesion within the abdomen. The injection of a local anesthetic solution into the abdominal wall may become both a diagnostic and a therapeutic procedure in cases of this type.

A quantity of dilute procaine solution should be injected over the point of maximum pain and tenderness. If a ruptured viscus is present, there will be little or no change in the objective findings or the patient's symptoms.

If the signs and symptoms have been caused by superficial trauma to the abdominal wall, the injection will produce immediate and marked relief.

Muscle Spasm

Two other areas where muscle strain and spasm may be extremely disabling are the neck and the arms. Involvement of the sternomastoid or trapezius muscles may cause a stiff neck with excruciating pain and great limitation of motion. The deltoid muscle, and particularly the area of its insertion into the humerus, is frequently subjected to trauma which produces disability. Injections of local anesthetic solutions into these muscles produce gratifying results.

Scalenus Anticus Syndrome*

The scalenus anticus syndrome may be caused by spasm or hypertrophy of the anterior scalene muscle, or less frequently by a cervical rib. The precipitating factor is often trauma. Because of its proximity to the subclavian artery and vein, the brachial plexus, and the cervical sympathetic chain, spasm or hypertrophy of the muscle may cause irritating pressure symptoms involving these important structures. Pain, tenderness, weakness, and vascular abnormalities of the arm and hand may occur; pain in the neck and chest may also be present. Injection of 2–5 cc. of procaine into the anterior scalene muscle produces complete relief of pain. If permanent relief is to be obtained, three or four injections may be necessary. If pain continues to return, transection of the muscle should be performed. The scalenus anticus muscle may be identified by pushing the sternomastoid muscle medially, pressing the fingers in behind the clavicular origin of the sternomastoid, and turning the patient's head to the opposite side. The scalenus anticus is then palpable.

Headache*

The causes and treatment of headache are numerous and a constant source of difficulty to the physician. When basic underlying diseases are ruled out, injection technics may aid in treatment, particularly if local tenderness on pressure is manifested. Occipital headaches may be caused by myositis of the semispinalis capitis and splenius capitis muscles or by occipital neuralgia. Myositis of the temporalis muscle and neuralgia of the auriculotemporal nerve may cause headaches involving the lateral aspect of the head. Myositis of the sternomastoid muscle may also produce upward radiation of pain. Frontal headaches may be caused by neuralgia of the supraorbital nerves. In each of these cases there is tenderness and pain radiating upward to the vertex. Injection of the involved area may cause complete disappearance of the local tenderness and the radiating pain. A single injection may be satisfactory, or its repetition on two or three occasions may be necessary.

* See also Chapter 11

* See also Chapter 22

Heart Disease

Many patients are partial or complete cardiac cripples, supposedly because of anginal pain and coronary disease Although tenderness is not usually associated with true anginal pain, some of these patients have painful areas in the region of the sternum and the anterior aspect of the thoracic cage Pressure on these areas may precipitate pain closely resembling a true anginal attack Trigger areas in the muscles of the chest may be demonstrated Infiltration of these trigger areas with local anesthetic solutions may stop an attack of so called anginal or pseudocardiac pain and reduce the frequency with which these attacks occur Most cardiologists believe that this type of tenderness and pain does not represent true coronary disease A few cases have been reported, however, in which coronary thrombosis was demonstrated by electrocardiogram and in which the pain could be relieved by injection of trigger points on the chest Symptomatic relief is desirable *whether or not true coronary disease is* present

PERIPHERAL NERVE BLOCK

The injection of local anesthetic drugs into or around large nerve trunks is called a nerve block To perform this procedure satisfactorily it is necessary that the physician be familiar with the location of the nerve trunk and the bony landmarks used to locate it The technics involved in nerve block are more difficult than those used for local infiltration The physician should not attempt to perform nerve blocks unless he has had training and experience The effort to learn nerve block procedures, however, is more than repaid by the increased ability of the physician to treat his patients

The drugs used for nerve blocks are the more concentrated aqueous or oil solutions of local anesthetics, 'efocaine,' alcohol, and specially prepared solutions of ammonium sulfate (sarapin') Particularly when using alcohol, accurate localization of the needle upon the nerve must be obtained Roentgenograms taken after placement of the needle are helpful in determining that the needle is in the proper location

Injection of the trigeminal nerve or its branches is valuable in treating tic douloureux and may also be used to provide relief from pain in patients with neoplastic disease of the face Cervical plexus blocks may be performed for painful conditions in the neck Hiccough may be stopped by injecting the phrenic nerves in the neck Injection of the brachial plexus with local anesthetics may be valuable in treating painful conditions of the arms and hands Injection of the intercostal nerves with water or oil solutions of local anesthetic drugs is of considerable value in treating intercostal neuritis, pleurisy, and trauma to the chest wall including fractures of the ribs Herpes zoster may involve almost any area of the body The severe pain in this condition may be offset by injection of the appropriate nerves as they emerge from the intervertebral foramina Injection of the sciatic nerve finds its principal use in the treatment of sciatic neuritis For painful conditions involving both lower extremities and the low back, caudal or epidural block is most practical because a number of nerves may be anesthetized with a single injection

Nerve blocks are most valuable when there is pain and tenderness of segmental distribution Injection of the nerve supplying the involved segment of the body frequently brings relief

SYMPATHETIC NERVE BLOCK

There are numerous diseases caused by or associated with, dysfunction of the sympathetic nervous system These diseases have as their principal manifestations, evidences of alteration in the circulation and in the nutrition of tissues, and pain In most cases

the etiology and the mechanism of progress of the disease are not definitely known It is postulated that regardless of the initiating factors an increase in the sympathetic tone or an imbalance of the sympathetic innervation finally occurs The increase in sympathetic tone causes vascular spasm and interference with the blood supply of the tissues

The signs of decrease in circulatory efficiency include diminished or absent arterial pulsation cyanosis coolness and edema Trophic disturbances are evidenced by thin glistening skin and nutritional changes in the bones and nails and a tendency to ulcerations that are slow to heal Increased perspiration is frequently present Pain in the extremity is one of the most common symptoms

Interruption of sympathetic innervation may be accomplished by injections of local anesthetic drugs into the sympathetic ganglia The usual areas selected for such injections are the stellate ganglion in the neck and the first second and third lumbar sympathetic ganglia Blocking the stellate ganglion interrupts sympathetic impulses of the arm neck and head blocking the lumbar sympathetic ganglia interrupts the conduction of impulses to the lower extremity A successful block is followed by dilatation of the vessels increased pulsation and warmth and decrease in sweating If the stellate ganglion is blocked the characteristic eye signs of the Horner s syndrome are produced

If widespread sympathetic denervation is desired it may be accomplished by the induction of spinal or caudal anesthesia causing interruption of nerve impulses in the preganglionic fibers

When injection technics produce satisfactory results but longer lasting effects are desired surgical excision of the sympathetic ganglia may be performed Unless the therapeutic aim is achieved by test sympathetic block it is often unwise to perform a surgical sympathectomy

Vasospastic Disease*

A variety of conditions may be included under the heading of vasospastic disease These include Raynaud s disease acrocyanosis frost bite trench foot and immersion foot Each of these conditions is accompanied by an unusual sensitivity to cold The normal response to cold is temporary vasoconstriction In these conditions the response occurs with only a slight lowering of the temperature The response is abnormal in nature intense and persistent and may become chronic Organic changes in the tissue may result from circulatory changes Interruption of the sympathetic innervation of the involved extremity may cause a remission in an acute process and may be of value in the treatment of the chronic condition

Thrombophlebitis

This is an inflammatory disease of the veins associated with vascular spasm apparently on a reflex basis Many of the symptoms are produced by vasospasm rather than by inflammation Most cases of thrombophlebitis involve the lower extremity though the arm may also be a site of this disease There is often dramatic relief of symptoms following block of the appropriate sympathetic ganglia The period of disability may be greatly reduced by this therapy Thromboangiitis obliterans and other inflammatory diseases of the blood vessels may also improve with this treatment

Vascular Occlusion

Injury to a blood vessel may be followed by organic occlusion of the vessel or by spasm If the injury involves the major blood vessels of an extremity there may follow such an impairment of the blood sup

* See also Chapters 11 and 23

ply as to result in gangrene of the extremity The picture frequently seen following such an injury is an extremity which is cold, blue, and pulseless An embolus lodging in a major artery produces similar results, because of occlusion and reflex vascular spasm

Interruption of the sympathetic innervation of the extremity is often an important measure in treatment If spasm of the vessels exists it will be relieved by a sympathetic block If the injury to the vessel has required ligation or if the vessel has been occluded, the sympathetic block causes dilatation of the collaterals the additional circulation provided may be sufficient to maintain viability of the limb and to eliminate the need for amputation

Following the block, the extremity becomes warmer the color improves, and a palpable pulse may be evident The improvement may be brief perhaps for only two or three hours, and the sympathetic block should be repeated as often as necessary to maintain the improvement Several injections may be required at intervals of two hours As the vascular channels improve the frequency of injection may be diminished although it may be necessary to continue them at intervals for several days A malleable needle or fine catheter may be left in place so that the block may be maintained by intermittent administration or slow continuous drip of anesthetic solution Close observation and repeated injection may result in the preservation of an extremity

Causalgia

This is a syndrome of severe pain that usually follows an injury The pain of causalgia appears to be out of proportion to the severity of the injury The etiology of causalgia has not been definitely determined Whether it is on the basis of an axone reflex caused by direct local stimulation or due to irritation or degeneration of an involved neural element, cannot be said with certainty Many of the patients suffering from causalgia appear to be hyperirritable or hypersensitive individuals Whether this is one of the predisposing causes, or a result of the intense pain is also open to question Personality changes occur frequently in patients who suffer from causalgia

It seems evident that the pain impulses in causalgia travel through the sympathetic nervous system Injection of the appropriate sympathetic ganglion may provide complete relief of the symptoms Sometimes repeated sympathetic blocks will provide a complete cure In many cases, however, the injection is followed by relief of symptoms for a relatively short period of time In these instances the relief following the injections is an indication that sympathectomy may be a valuable therapeutic procedure

Miscellaneous Conditions

Sympathetic blocks are also helpful in the treatment of other poorly understood conditions Trophic ulcers, hyperhidrosis, lymphedema post traumatic edema, limitation of motion following prolonged immobilization Sudeck s atrophy, early arthritis the shoulder hand syndrome and phantom limb pain may be cured or greatly improved by interruption of the sympathetic innervation of the part Beneficial results have been obtained by stellate ganglion block in cases of detached retina when the viability of the retina was threatened because of poor blood supply Asthma and anginal syndromes may also be relieved Symptoms of a pulmonary embolus may be greatly relieved by sympathetic block, which interrupts the reflex vasospasm Ureteral colic may be treated by lumbar sympathetic block which causes relaxation of the spastic ureter and relief of pain If a small ureteral stone is present, it may be passed when the spasm of the ureter is relieved

Cerebral Vascular Accidents

These have recently been added to the field of injection therapy When a cerebral vascular accident occurs there is impairment of the blood supply of the brain and associated symptoms of neurologic dysfunction In many cases dysfunction is greater than can be accounted for by the organic lesions It is postulated that there is associated spasm of adjacent vessels resulting in a greater decrease in blood supply to the brain and an increase in the symptoms Episodes of cerebral vascular spasm may occur without a classical cerebral accident The spasm results in a slowing of the flow of blood and may eventually be followed by thrombosis of the involved vessels

A block of the stellate ganglion on the same side as the lesion is of value in relieving cerebral vascular spasm If the spasm occurs without an organic change in the vessel the stellate ganglion block provides a rapid relief from symptoms When there is associated organic change in the blood vessel the symptoms will be relieved to some extent If the lesion is thrombosis or embolism stellate ganglion block should be performed at the time of diagnosis When a cerebral hemorrhage is diagnosed it may be wise to allow a number of hours for hemostasis to occur before the block is performed Rapid improvement may be noted though there may be a regression within a few hours and the block should be repeated as often as necessary to maintain symptomatic improvement The reduction of vascular spasm and the increase of the blood supply to the involved areas of the brain will reduce the extent of residual brain damage

Acute Pancreatitis*

The symptoms of this condition may resemble those of acute cholecystitis or perforated peptic ulcer One of the diagnostic features is elevation of the blood amylase level The patient usually has severe abdominal pain Although the rationale of the procedure has not been clarified symptomatic improvement frequently is dramatic when the splanchnic nerves are blocked The intense pain disappears with perhaps some soreness remaining

* See also Chapter 17

SPINAL ANESTHESIA

Essential Hypertension*

This condition is sometimes treated by surgical means In selecting patients for operation anesthetic technics may be used for diagnosis and prognosis If hypertension is caused principally by vasospasm the interruption of sympathetic impulses relieves the spasm and produces a lowering of the blood pressure If organic changes in the vessels predominate as the cause of the hypertension interruption of the sympathetic impulses does not substantially lower the blood pressure Interruption of the sympathetic innervation of the blood vessels therefore is of value in differentiating between vascular disorders of organic and vasospastic origin The sympathectomy operation serves to denervate the vessels and produce vascular dilatation followed by a drop in blood pressure

A functional sympathectomy may be performed by the induction of either caudal or spinal anesthesia The injection of the anesthetic drug causes paralysis of the preganglionic sympathetic nerves and produces a situation analogous to that caused by a sympathectomy The blood pressure graph obtained following the administration of the anesthetic provides probably the most reliable aid in prognosis prior to sympathectomy A marked and sustained fall in blood pressure indicates that good results may be expected from the surgical procedure If continuous spinal or caudal anesthesia is used it is possible to study the blood pressure response to varying heights of anesthe

* See also Chapter 5

sia with increasing extent of sympathetic paralysis

Acute Hypertension*

Episodes of acute hypertension may occur in toxemia of pregnancy and acute nephritis Convulsions, coma, cerebral vascular accidents, and severe disturbances of urinary output may occur Although hypertension is not the cause of the disease, it is one of the important symptoms If the hypertension is reduced improvement frequently occurs

An effective means of controlling the hypertension in these cases is to block the sympathetic innervation of the blood vessels by inducing spinal or caudal anesthesia For the production of a sustained drop in blood pressure, continuous or fractional methods of anesthesia may be applied Continuous spinal or caudal anesthesia may be maintained for several days, holding the blood pressure at safe levels Meanwhile, the physician may apply other therapy to correct the basic disturbance

Cardiac Failure†

Acute cardiac failure and acute pulmonary edema on a cardiac basis may occur *suddenly* The usual methods of drug therapy require some time before becoming effective Phlebotomy and the application of *tourniquets to the extremities produce* a more rapid therapeutic response, by reducing the return flow of blood to the heart so *that pulmonary congestion is diminished* The induction of low spinal anesthesia with the patient in a sitting position produces a similar result *Following* spinal anesthesia, there is a pooling of blood in the lower extremities diminishing the return flow of blood to the heart *In effect, a bloodless* phlebotomy is performed Following the induction of spinal anesthesia in these patients, dramatic improvement may *occur*, during this time rapid digitalization may be accomplished

* See also Chapter 15
† See also Chapter 10

Lower Nephron Nephrosis*

This condition was included in the scope of anesthetic therapy when it was found that *anuria following sulfonamide medication* or transfusion reaction could be effectively treated by spinal anesthesia Lower *nephron nephrosis* is a complex condition that is poorly understood Kidney pathology results in anuria or oliguria, uremic manifestations occur and death may follow

Many etiologic factors may be mentioned *Injury to the kidney, alkalosis toxemia of* pregnancy, shock, transfusion reactions and reactions to sulfonamides Anoxic damage to the kidney is probably the basic mechanism The tubular epithelium is damaged The lumen of the tubules may be filled with sulfonamide or hematin crystals myoglobin, or cellular debris, and there is failure of the selective absorption function of the tubules Tubular regeneration occurs if treatment is successful Vascular spasm and arteriovenous shunts take place within the kidney A neurohumoral mechanism is proposed in explanation of this complex condition

Treatment The treatment of lower nephron nephrosis has two aims to maintain the fluid and chemical balance of the patient, and to restore the function of the kidneys Fluids administered to the patient should be adequate to replace the extra renal fluid loss The administration of large amounts of fluid to promote diuresis does no good and may produce edema and cardiac failure The type of fluid administered should be determined by careful blood chemistry analysis, and should maintain the electrolyte balance and provide carbohydrate for metabolic purposes Gastric and peritoneal lavage and the artificial kidney are used to rid the body of substances ordinarily excreted by the kidney

* See also Chapter 18

Spinal and caudal anesthesia may be of value Interruption of the sympathetic nerve supply to the renal vessels favorably influences the circulation of the kidney Increased urine output may follow The continuous or fractional method of spinal or caudal anesthesia should be used so that prolonged treatment may be instituted The level of anesthesia should be high enough to block the splanchnic nerves which supply the innervation of the renal vessels

Pain of Cancer

So far little progress has been made in the relief of pain in patients who have incurable cancer At present the methods available for relieving these patients are neurosurgical operations or the administration of opiates For many reasons neurosurgical procedures are performed on only a small proportion of the patients When opiates are used increasingly large doses are required and they are often inadequate * The anesthetist attempts to contribute to the treatment of these patients by nerve blocks or intrathecal administraion of alcohol or ammonium sulfate The intrathecal injection of alcohol causes destruction of the nerves bearing pain impulses Accurate diagnosis of the segmental levels involved is necessary A method of alcohol administration has been described using a catheter in the spinal canal which utilizes accurate placement of small amounts and decreases complications

The intrathecal injection of specially prepared solutions of ammonium sulfate may bring pain relief for a period of a few weeks to several months The procedure is most valuable when tenderness of segmental distribution can be demonstrated From 0 2 Gm to 0 4 Gm of ammonium sulfate diluted with a large quantity of spinal fluid is injected A period of acute distress frequently follows with nausea retching and pain this can be prevented by simultaneous administration of light pentothal anesthesia The procedure is not effective in every case, and there is an appreciable incidence of complications

Solutions of ammonium sulfate may be used for caudal anesthesia and for nerve blocks The injection of the drug is painful and should be preceded by injection of procaine solutions Prolonged pain relief may be obtained by this means

* See also Chapter 22

REFRIGERATION

When injury to an extremity results in an impairment of its blood supply so that gangrene may occur and amputation become necessary, therapy should be based on the following principles increase of blood supply by sympathetic block which produces relief of vasospasm and increase of collateral circulation and reduction of the oxygen requirement of the tissues so that viability may be maintained in spite of impaired circulation Reduction of the oxygen requirement of the extremity may be achieved by decreasing its temperature

The wound should be debrided and covered with a sterile dressing and towel The extremity should then be cooled without a tourniquet Two layers of blankets should be placed upon a flat surface and covered with a rubber sheet Pieces of ice which have been cracked to approximately 2 5 cm in diameter should be spread on the rubber sheet to a thickness of 10 cm The extremity should then be placed on the layer of ice and the edges of the rubber sheet and blankets raised Additional ice is then added as the rubber sheet and blankets are raised and finally folded over The extremity should be completely encircled by a 10 cm thickness of ice The proximal end of the injured extremity should be higher than the distal end. At the distal end the rubber sheet should be arranged to form a funnel so that the water from the melting ice runs down into a bucket upon the floor The ice should be replenished as often as necessary

No tourniquet should be applied to the xtremity unless amputation is decided ipon Ordinary water ice should be used, arbon dioxide or 'dry ice' causes too great a lowering of the temperature, and will cause freezing of the tissues Ice and salt mixtures should not be used for the same reason A refrigeration device is available to accomplish cooling without the use of ice It is not desired to freeze the tissue, the aim is to cool the tissues to a point where metabolic requirements are reduced It may be necessary to maintain this form of cryotherapy for a number of days

INTRAVENOUS PROCAINE

The intravenous injection of local anesthetic drugs has in the past been regarded as a very dangerous procedure This is because the injections were inadvertently performed the concentration of the drug was great and the speed of injection was rapid As a result the patient received a massive dose of local anesthetic drug intravenously and toxic symptoms developed

The intravenous injection of procaine is a relatively safe procedure when certain precautions are followed The drug should be administered in an infusion so that its concentration is reduced One gram of procaine (5 cc of 20 per cent solution) is added to a liter of infusion fluid—either isotonic sodium chloride solution or dextrose We have found it desirable to also add 0 1 Gm of sodium pentothal The entire quantity may be administered over a period of sixty to 90 minutes An alternative procedure is to use a dose of 4 mg of procaine per Kg body weight and to administer the infusion in a period of twenty minutes The patient should be carefully watched for symptoms of toxicity If these occur the rate of the infusion should be reduced The symptoms of toxicity that may develop following the intravenous injection of procaine are the same as those previously described

Another safety factor in the intravenous injection of procaine is that the drug is rapidly destroyed after injection Reduction of the rate or cessation of the administration is rapidly followed by a diminution or disappearance of the toxic symptoms

Sodium pentothal should always be available for administration so that toxic symptoms may be treated if necessary Minor toxic symptoms occur often enough to be disturbing They may be prevented by the addition of 0 1 Gm of sodium pentothal to a liter of solution which contains 1 Gm of procaine This quantity of pentothal produces no symptoms, though it may cause the patient to become slightly drowsy

The mechanism of action of intravenous procaine is probably based on increased capillary permeability Areas of injury or inflammation have some capillary damage resulting in increased permeability It is postulated that procaine administered intravenously tends to concentrate in these areas of increased capillary permeability and reduces the pain

Procaine has been administered intravenously in the treatment of numerous painful conditions such as arthritis myositis fibrositis, and in posttraumatic conditions of the muscles, bones, and joints In patients who are severely burned intravenou procaine provides analgesia without the u of large quantities of narcotics After oper tions the pain may be reduced by the ministration of intravenous procaine P relief may also be provided in this man for patients who have fractures and ot injuries

Intravenous procaine is valuable in treatment of some allergic disorders ticularly serum sickness The prurit jaundice is relieved contact and exfol dermatitis improve some peripheral lar conditions are benefited by intra procaine administration When car rhythmias occur during surgical ane the administration of procaine

nously may re establish normal rhythm Anuria and oliguria resulting from lower nephron nephrosis may be treated in this manner Intravenous procaine has been used and recommended in numerous other diseases

MUSCLE-RELAXING AGENTS

Curare*

The anesthesiologist is familiar with muscle relaxing drugs because of the need for muscular relaxation during surgery Recently, means have been found to produce relaxation without deep surgical anes thesia Curare or its derivatives are most commonly used for this purpose These *drugs act by interfering with the transmis sion* of impulses at the junction of the nerve and the muscle Curare must be adminis tered by injection orally it has no effect

Curare has been used in the treatment of diseases associated with muscle spasm, the outstanding examples being poliomyelitis and tetanus Numerous reports have indi cated that curare is useful in preventing or reducing the severity of convulsive seizures in tetanus Curare reduces the muscle spasm of poliomyelitis and it has been stated that pain is relieved and that residual deformity is reduced For use in these conditions curare has been prepared in an oil solution Intramuscular administration of this prep aration provides muscle relaxation for many hours

When shock therapy is administered in psychiatry, the convulsions produced may be severe enough to cause fractures The ad ministration of curare prior to the shock treatment reduces the severity of the con vulsions and prevents the occurrence of fractures

Curare is useful for a diagnostic test in patients with myasthenia gravis, particu larly those with mild symptoms The dis ease is associated with unusual susceptibility to curare small doses of the drug intensify the symptoms of myasthenia gravis If the patient s symptoms are increased following the intravenous administration of 0 1–0 5 cc of curare, the diagnosis is confirmed Fol lowing a positive test, the effect of curare should be overcome by the intravenous ad ministration of 1 5 mg of prostigmine and 0 4 mg of atropine

Apparatus for administration of artificial respiration with oxygen should be avail able A laryngoscope, an endotracheal tube and a person familiar with their use should be present Deaths have occurred fol lowing curare administration because of pa ralysis of the muscles of respiration

* See also Chapter 22

Mephenesin

Mephenesin is a synthetic drug having muscle relaxing properties It differs chem ically from curare, and its site of action is in the basal ganglia thalamus brain stem, and spinal cord where it interferes with the transmission of impulses Mephenesin is effective when administered orally, oral preparations are available Oral administra tion of this drug results in a diminution of muscular spasticity but it does not interfere with voluntary motion It has proved of some value in the treatment of such condi tions as Parkinson's disease, cerebral palsy, and delirium tremens The drug has marked sedative action and may cause unexpectedly severe sedative action when used in combi nation with barbiturate anesthesia

45. Physical Therapy in Treatment

EDWARD M KRUSEN, JR.
& FRANK H. KRUSEN

PHYSICAL medicine has been defined as the employment of the physical and other properties of light heat cold water, electricity massage exercise and mechanical agents for the diagnosis or treatment of disease The term physical medicine has replaced physical therapy because of the increasing use of physical agents in diagnosis and because of the inclusion of occupational therapy and rehabilitation in this specialty

The scope of physical medicine is broad The several physical agents used in a multitude of different combinations can be applied to the diagnosis and treatment of a large number of diseases Although it is a mistake to recommend physical medicine indiscriminately physical measures can be of great help in a large number of diseases especially the chronic diseases for which there are no specific cures In these the objective of treatment is maximal restoration of function

It should be borne in mind that dangers underlie the improper use of the physical agents their unscientific employment does not produce the desired effects and leads to erroneous impressions as to their usefulness Undoubtedly some of the distrust of physical medicine that many physicians have displayed has been due to its exploitation by charlatans and irregular practitioners Physical medicine should be under the immediate direction of a physician who understands the diagnosis the structural or functional changes resulting from the condition being treated and the individual tolerance of the patient As the patient s condition improves the physician must know what alterations in treatment should be made Changes or discontinuation of treatment should not be the responsibility of the patient or of the therapist treating the patient

The physical agents most commonly employed in the treatment of diseases will be discussed in the following order Thermal measures ultraviolet radiation massage therapeutic exercise occupational therapy spa therapy and rehabilitation

Thermal Measures

THE primary physiologic effects of heat are relief of pain, release of spasm and increase in circulation By increasing the supply of blood to the treated region heat increases exchange of oxygen and hastens the absorption of exudates It also increases metabolism locally or generally depending on the extent of application Since the increase in circulation is mainly on the arterial side, an increase in swelling may result unless the venous return is adequate

MEANS OF APPLICATION

There are several means by which heat may be applied both locally and generally These include (1) the conductive method in which heat is applied by direct contact between the heated object and the body (2) the convective method in which heat is directed on the surface of the body from a distant source for example a heat lamp and (3) the conversive method, in which heat is produced in the body tissues by the resistance offered by the tissue to the passage of high frequency electric currents

Regardless of the method employed the physiologic effects of heat are the same The method used depends on the depth of heat penetration required the area to be treated the convenience of the method and the response of the patient As a rule heat should be applied for at least thirty minutes since the maximal heating effect is not attained in less than twenty to thirty minutes

Conductive Heat

Devices commonly used for the production of conductive heat include electric pads applications of hot solids or semisolids, such as paraffin and application of hot water

Electric Pad The electric pad has a rather limited therapeutic usefulness because of the consumption of time if multiple areas are to be treated the danger of burns, and the danger of shocks if the patient perspires freely For use of the patient at home an inexpensive heat lamp, which is discussed later, is more effective and safer to use

Paraffin The application of hot paraffin is an excellent method for treating small areas of the body such as the hands or feet Its chief advantages are that it holds heat well, entirely surrounds the part produces good hyperemia, and leaves the skin soft and pliable In institutions a thermostatically controlled bath is used in which the paraffin is maintained at a temperature of approximately 130° F The extremity is dipped several times into the paraffin to form a coating and can then be left to remain in the bath for thirty minutes When such a unit is not available the following simple method can be used equally effectively

The paraffin is melted in a double boiler and allowed to cool until there is a thin film on top The part is dipped into the paraffin several times until there is a covering about 3-6 mm thick then it is wrapped in towels for at least thirty minutes After the treatment the paraffin can be removed and placed in the double boiler for reheating To facilitate its removal from hairy surfaces it is advisable to mix mineral oil with the paraffin in proportion of 1 to 7 or to apply mineral oil to the surface before the application of paraffin

The melted paraffin can also be applied with a paint brush until a layer of satisfactory thickness covers the part This covering is left in position for thirty or more minutes Paraffin dressings in the form of alternate layers of paraffin and bandage

may be used where support is desired for example, on a wrist

Application of paraffin is excellent in the treatment of *rheumatoid arthritis* and *osteo arthritis* involving the hands or feet and in the follow up treatment of *hand injuries* with residual stiffness preceding exercises to increase motion

Paraffin should not be applied over open lesions or anesthetic areas Very rarely a transitory dermatitis will develop on application of paraffin In these cases this method should be discontinued and another form of heat substituted

Wet Packs Hot wet packs are another method of applying conductive heat Some patients tolerate this form of heat best It is advisable not to exceed a temperature of 120° F if the packs are not completely *wrung out* Usually hot packs do not remain warmer than body temperature for more than fifteen to twenty minutes Therefore unless the hot wet packs can be changed frequently it is advisable to avoid this method of conductive heating

A special type of hot wet pack is the so called *Kenny pack* used in treatment of poliomyelitis These packs consist of a layer of wool boiled in water or steamed wrung and laid on the part covered with another layer of dry wool and insulating material In severe cases of acute anterior poliomyelitis with respiratory involvement hot packs should not be employed unless utilized to make respiration easier Once this crucial stage has passed or when there is less severe involvement relief of pain and prevention of deformity become of first importance Hot packs applied for four to six hours daily and changed every half to three-quarters of an hour often will help relieve pain Prone packs large enough to cover the entire extremities—and if necessary the back also—save time Small children however may require individual packs for each part to be treated As soon as the patient can be moved easily, warm tub baths should be substituted

Baths *Whirlpool baths* are a commonly used local bath for treatment of arms or legs The extremity is immersed in the bath for thirty minutes at temperatures from 100 to 110° F The heat and gentle massage of the whirlpool stimulate circulation relax muscles relieve pain and form an ideal preparation for exercise This form of bath is particularly effective in the treatment of fractures after removal from the cast of sprains or strains after the first twenty four hours, postoperative skin grafts indolent wounds and nerve lesions One objection to whirlpool baths is the possibility of increased swelling due to the dependent position of the part treated

The *contrast bath* is another form of local bath It consists of alternate immersion of the part to be treated in hot (105–110° F) and cold (60° F) water The treatment is always started and ended by placing the part in hot water The greatest elevations of cutaneous temperatures are obtained when the part is first immersed in hot water for ten minutes then in cold water for one minute and in hot water for four minutes for three to four alternations the immersion always ending in hot water Contrast baths are especially useful for home treatment of *rheumatoid arthritis* and *osteoarthritis* The extremes of temperature should not be used if there is any circulatory disturbance

Generalized warm or hot baths are used to produce general heating and relaxation in preparation for exercises They may be given in an ordinary bath tub or in a Hubbard tank which permits exercises at the same time The temperature of the bath is kept at 100–101° F for the treatment of poliomyelitis patients or patients with extensive burns

If an elevation of body temperature is desired the temperature of the water is gradually raised from 98° to 104–105° F

over a period of thirty minutes This usually raises the temperature of the body to approximately 101° F Such short fever sessions are employed in the treatment of *rheumatoid arthritis* and *spondylitis* in conjunction with other physical measures Hot tub baths or fever cabinets may be employed equally effectively An increase in peripheral blood flow results which is greater than that produced by the injection of typhoid vaccine The patient usually can tolerate such treatments daily and often with considerable benefit A gradual increase of the bath temperature tends to decrease undesirable side reactions The final temperature of the bath should be varied to conform to the general health of the patient Hot baths should be prescribed cautiously for patients more than 60 years of age, and for those who have conditions which contraindicate elevation of bodily temperature

Considerable fluid is lost through perspiration if the body temperature is raised and the patient should receive one to two glasses of water during the treatment or preferably one to two glasses of 0 3 per cent solution of sodium chloride

Convective Heat

The devices commonly employed to produce convective heating are heat lamps and luminous bakers These devices can be simple, easy to use and satisfactory both for office and home treatment

Lamps The type of lamp used depends on the wavelength desired for heating All heat lamps produce infrared radiation Until recently it has been considered that lamps which produce a greater proportion of the shorter infrared rays have a deeper penetration than lamps which produce a greater proportion of the longer infrared rays For this reason lamps with carbon or tungsten filament bulbs have been considered superior to infrared generators consisting of wires coiled around porcelain or carborundum cores While recent research seems to indicate that this belief is fallacious luminous lamps with bulbs of the carbon filament or tungsten filament type are still generally preferred

Lamps are effective in the treatment of small areas The maximal heating effect of a lamp is confined to a central area with the intensity falling off rapidly toward the periphery Large lamps with 1500 watt tungsten filament bulbs in large reflectors are effective in treating large areas like the back For smaller areas small 250 watt heat bulbs are satisfactory Such bulbs in which a reflecting surface is incorporated can be attached to a clamp holder and supply an inexpensive source of heat for home use The distance from the lamp to the part to be heated varies from 45 to 60 cm according to the heat tolerance of the patient

Bakers A more uniform type of heating is that produced by luminous bakers These devices, consisting of curved metal reflectors with four to twelve bulbs of either the carbon filament or tungsten filament type attached can be used either singly or in tandem to cover large areas of the body A general elevation of cutaneous temperature is produced if two large bakers are applied for thirty minutes There also may be a slight elevation in bodily temperature which usually is tolerated well

Lamps and bakers may be used in all conditions in which heat is indicated They should not be used where deep heating is preferred since infrared rays only penetrate to a depth of 3–5 mm

Bakers singly or in tandem are particularly useful in treating multiple areas as is frequently necessary for patients with *osteoarthritis rheumatoid arthritis*, or *rheumatoid spondylitis*

For the treatment of hands and feet alone the use of the conductive methods such as paraffin or contrast baths is preferred to either lamps or bakers since only a portion

of the surface of these parts of the body can be exposed to the heat source if infra red radiation is used

Conversive Heat

The devices for the production of conversive heat provide long wave diathermy, short wave diathermy, and microwave diathermy The only physiologic effect of these devices is that of heat but the main advantage is the much deeper penetration of heat than that resulting from other means

Long wave Diathermy Long wave diathermy is produced by high frequency electrical apparatus of the spark gap type The current of this machine oscillates between 100,000 and 10 000 000 times per second and is of comparatively long wavelength (30–3000 meters) This machine has become obsolete because of regulations by the Federal Communications Commission prohibiting its use after July 1952

Short wave Diathermy Short wave diathermy is produced by machines with vacuum oscillators The wavelength of the radiation produced by the short wave diathermy machine is between 3 and 30 meters with a frequency of 10 000 000 to 100 000 000 cycles per second

Short wave diathermy is usually applied by means of cables drums, or air spaced electrodes If a cable is employed it is necessary to provide proper air spacing in the form of toweling 2–4 cm thick Drums are constructed so that there is adequate air space and they may be applied directly to the skin with only one layer of toweling to absorb perspiration Air spaced electrodes can be applied on opposite sides of the part to be treated or both may be applied on one side

Microwave Diathermy Microwave diathermy is an adaptation of radar and is produced by a multicavity magnetron tube The wavelength ranges from 1 millimeter to 1 meter at frequencies of 300 million to 300 000 million cycles per second The radiation is conducted from the tube to the director by means of a coaxial cable The distance from the director to the surface of the body varies with the type of director and the output used No toweling is required and application is simple and convenient

Applications of Diathermy Diathermy provides deeper penetration than any other form of heating and is therefore the agent of choice when deep heating of tissues is indicated The more commonly encountered indications are Osteoarthritis involving especially the hip or knee, bursitis fibrositis and myositis, sprains and strains, sinusitis, pelvic inflammatory disease, and certain types of backache

Microwave diathermy produces more localized heating than does short wave diathermy For this reason, its application is somewhat more limited It has been found to be especially effective in the treatment of *shoulder* conditions, such as periarthritis, bursitis or tendinitis Tendinitis or bursitis in other locations and localized fibrositis can also be effectively treated by microwave diathermy If there is an increase of fluid in the area exposed to microwaves there may be excessive heating of the fluid causing an increase in pain In these cases microwave diathermy must be discontinued

In general diathermy is not applied conveniently in rheumatoid arthritis because the treatment of multiple joints is time consuming and because the simpler methods mentioned previously are more practical Occasionally the acutely swollen joints in rheumatoid arthritis are intolerant to diathermy, causing an increase of pain during treatment and it may be necessary to use other forms of heat Similarly diathermy frequently is tolerated poorly in neuritis Diathermy should not be used early in the treatment of fractures since the marked increase in circulation may produce an increase in soft tissue swelling and decalcification of bone

Safeguards During Diathermy. Several important precautions should be taken when diathermy is used The cable or electrode always should be kept more than 30 cm from a spring or innerspring mattress since closer application may cause sufficient heating of the metal to produce a fire hazard Also no metal implants should be in the electromagnetic field of the applicator Diathermy is also contraindicated to regions where a malignant tumor is suspected or where there is danger of producing or increasing hemorrhage To prevent burns, diathermy should not be applied over adhesive strapping or to areas which are anesthetic or ischemic

A special diathermy technic has been developed for *peripheral vascular diseases* The application of any form of heat in the presence of peripheral vascular disease is not without danger Excessive heat which usually would be dissipated by tissues with normal circulation results in burns and gangrene in tissues with poor circulation For this reason hot water bottles and electric pads *should not be applied directly to* extremities with poor circulation A simple baker with a small output of heat may be placed over extremities but ideally heating devices applied directly should be thermostatically controlled to maintain the environmental temperature at 90° F and certainly not exceeding 100° F Reflex vasodilatation by means of shortwave diathermy is a satisfactory method of increasing blood flow to the lower extremities In this technic diathermy is applied to the lumbosacral region for a period of thirty to sixty minutes with the extremities covered

Diathermy should not be employed in home treatment While portable diathermy machines are available, no physician should take the responsibility for home treatment with these machines Many blunders may occur in untrained hands and satisfactory results can be obtained with simpler and safer apparatus

Ultrasonic Diathermy. A new form of diathermy—ultrasonic diathermy—has been developed in Europe and is being studied in this country The high frequency sound waves are produced by utilizing the magnetostriction effect on a quartz crystal The energy is applied to the surface of the body by means of a sound head and coupling substance Enthusiastic claims of clinical results have been reported in the European literature However, careful *investigations* in this country have indicated grave dangers connected with this form of energy Damage to nerves, spinal cord, growing bone, and numerous other tissues has been demonstrated For this reason ultrasonic diathermy is not considered safe for clinical use at the present time

Ultraviolet Radiation

ULTRAVIOLET energy is a form of radiant energy similar to infrared and visible light energy The wavelength of ultraviolet energy is shorter than those of visible light and infrared radiation The ultraviolet portion of the spectrum is divided into two parts, similar to the division of the infrared spectrum The 'far" ultraviolet rays especially the wavelengths from 200 to 280 mμ have actions that are primarily bactericidal and produce destruction of tissue The near" ultraviolet rays, between 290 to 390 mμ produce photochemical changes in the skin, characterized by latent erythema and pigment, and bring about the conversion of provitamin into

vitamin D The near ultraviolet energy is more commonly used therapeutically

It is generally produced by the hot quartz mercury vapor arc lamp The new type of hot quartz lamp consists of two tungsten electrodes a rare gas to produce the initial arc and a small amount of mercury that vaporizes to form the mercury vapor arc This lamp produces a complete ultraviolet spectrum plus visible and infrared rays with a good output of energy in the region of the 290–330 mμ band This is the most practical therapeutic lamp for use in a hospital or physician s office

CLINICAL APPLICATIONS

The dosage of ultraviolet radiation is based on its physiologic effect on the skin This effect is the development of an ery thema on the untanned skin of a person with average pigmentation The duration of exposure which is necessary to produce an erythema at a given distance between lamp and skin is called the "minimal ery themal dose or M E D When a physician prescribes ultraviolet radiation, the dosage should be given in terms of minimal ery thernal dose With newer models of the hot quartz mercury vapor arc lamps the mini mal erythemal dose is approximately thirty seconds at 75–90 cm However this M E D must be determined for every source of ul traviolet radiation and should be redeter mined at intervals of three months, since the sources of ultraviolet rays tend to de teriorate with use

Clinically, the greatest value of ultravio let radiation is in the treatment of certain skin conditions These include acne alo pecia areata, dermatitis herpetiformis der matophytosis, eczema, folliculitis, pityriasis rosea, tuberculodermas chronic ulcers and wounds, and psoriasis

For most conditions, the initial dose should be 1 M E D and should be increased by 1 M E D with each succeeding treat ment Treatments should be given three times a week In most instances ultraviolet irradiation cannot be given daily because of the cumulative effect on the skin Larger doses are indicated in the treatment of in dolent wounds and cutaneous tuberculosis When ointments with an oily base are used the rays will not penetrate well through the film and daily treatments are indicated A special technic has been developed by Goeckerman for the treatment of psoriasis and psoriatic arthritis In this method 2–6 per cent ointment of White s crude coal ta[r] is applied to the entire cutaneous surfac[e] except the nails on the day before trea[t] ment In the morning before treatment wi[th] ultraviolet light the coal tar is smooth[ed] out with olive or cotton seed oil to a th[in] film Ultraviolet light is applied to t[he] whole body including the areas free lesions

Contraindications to the use of ultra[vio] let radiation include dangers of exce[ssive] sunburn, possibility of a carcinogenic ef[fect] danger of flaring up conditions like l[upus] erythematosus, hyperthyroidism and [dia] betes The eyes should always be prot[ected] during exposure to ultraviolet radiat[ion]

Massage

THE primary physiologic effects of massage are an increase in the flow of lymph from the massaged part and a stimulative or seda tive effect on sensory nerve endings

In general three movements a[re used] therapeutically the stroking, knead[ing and] friction movements Stroking mas[sage con]sists of long smooth movements of [the]

over the skin Kneading consists of gently picking up, rolling squeezing and wringing of muscles Bland mineral oil or talcum powder is the lubricant of choice Medicated lubricants are of little value and occasionally may be harmful Friction consists of circular movements of the tips of the fingers pressed firmly into the indurated parts No lubricant is used

Stimulative massage, consisting of hacking clapping pounding and similar movements although practiced at many spas, has no place in the treatment of diseases

CLINICAL APPLICATIONS

Massage generally is not effective by itself in the treatment of most conditions and usually should be preceded by heat and followed by exercise Stroking and kneading massage is indicated for the relief of pain muscle spasm, or swelling associated with numerous musculoskeletal diseases and injuries

Friction massage forms an essential part of the treatment of subacute and chronic fibrositis Ordinary stroking and kneading massage alone is of little value Extremely heavy local friction massage must be applied over the indurated areas or nodules The pressure of the massage is adjusted to the tolerance of the patient but it is gradually increased as pain decreases Friction massage is also used in loosening tight scar tissue

Contraindications to the use of massage are the presence of tumors infections, or skin lesions

It is well to remember that massage by itself does not increase muscular strength Only active exercise can produce the muscular strength necessary to overcome deformity and maintain function

Therapeutic Exercise

THERAPEUTIC exercise has become one of the most important procedures in physical medicine It can be simply defined as the application of bodily movement in treatment of disease or malfunction But extensive basic knowledge is necessary to use bodily motion adequately and the one who accepts the responsibility of prescribing and supervising therapeutic exercise should have knowledge of mechanical biochemical and biologic laws in relation to mechanical efficiency and malfunction

The most common errors in prescription of exercise are lack of precise instruction failure to observe the patient, insufficient dosage of exercise, and inadequate adjustment of the exercise to the changing status of the patient

Some of the important physiologic effects of exercise are increase in circulation, increase in muscular strength prevention of muscular atrophy and decalcification of bone, and assistance in maintaining normal range of motion of joints and in establishing patterns of motion

Therapeutic exercise is generally classified into passive exercise, active assistive exercise, active exercise, and active resistive exercise

PASSIVE EXERCISE

Passive exercise is that form of bodily movement which is carried through by the operator without the assistance or resistance of the patient Usually this type of motion should be within the limit at which pain occurs and should be stopped when muscular spasm begins Passive exercise does not increase muscular strength and is prescribed only to retain full movement of

joints in cases of paralysis or in cases in which active muscular contraction is contraindicated

Active, voluntary purposeful movements are of vital importance in restoring the normal neuromuscular mechanism since they are initiated by mental processes and affect the upper and lower motor neurons, motor and sensory nerves the myoneural junction and muscle itself Nothing else can influence the neuromuscular arc so exclusively and favorably

ACTIVE ASSISTIVE EXERCISE

In active assistive exercise the patient makes an active effort to move the part and assistance is given by an outside force This exercise is prescribed when there is stiffening of joints to obtain increased range of motion When assistance is given by a therapist to increase joint motion the amount of desired forcing must be carefully prescribed It is also ordered when muscle power is deficient, to assist in re-education and strengthening until active free exercise can be performed Assistance may be supplied by a therapist or by certain procedures that tend to lessen gravity and friction such as a powdered board a sling suspension pulleys or underwater exercises

FREE ACTIVE EXERCISE

Free active exercise is any purely voluntary movement without external resistance or assistance It is prescribed primarily for maintenance of normal range of motion prevention of atrophy and strengthening and re education of muscles Static or isometric muscular contraction termed *muscle setting* does not involve any joint motion It is prescribed to maintain circulation and tone when motion of joints is impossible or contraindicated

RESISTIVE EXERCISE

Resistive exercise is that form of active exercise where resistance is offered to motion by an external force Resistance may be applied manually or by lifting measured weights Correct resistance may be the best way to make one muscle group work alone and exclude its antagonists Proper resistance also permits graduated muscular work to increase strength It must be remembered that low resistance and frequent repetition of exercise increase endurance but not power Increased resistance and infrequent repetition of exercise increase power and lead to hypertrophy of muscles This principle is applied in progressive resistive exercises, in which progressive increase of resistance is applied to a given muscular activity

EXERCISES FOR SPECIFIC CONDITIONS

Therapeutic exercise is undoubtedly more important than other physical agents in the treatment of many conditions The specific exercises for a number of common conditions will be discussed in some detail Exercises in the treatment of arthritis will be found in Chapter 26

Backache

The purpose of exercises in the treatment of most conditions causing backache is to restore as completely as possible the normal function of the spinal structures Normal function depends on proper alignment of these structures and on normal support by the ligaments and musculature Chronic back strain may result from long continued faulty posture alone An acute strain may occur in a normal back subjected to an unusual force or in a back with poor function that has been subjected only to minor injury

The physical treatment of acute strain consists of rest on a firm mattress with fracture boards and heat, and light massage As soon as the acute pain and muscular spasm have subsided exercises should be started to restore function The exer

cises should emphasize development of the gluteus maximus and the abdominal muscles Contraction of the gluteal muscles ten times an hour can be begun in bed The abdominal muscles can be strengthened by raising the head and shoulders from the bed about five times each hour The number of repetitions is gradually increased as the tolerance of the patient permits Flexion of the lumbar spine is done in the supine position by raising one knee at a time to the chest After the acute stage both knees may be raised simultaneously

The patient is also taught to stand correctly with the feet pointed straight ahead the pelvis tilted backward with the gluteal and abdominal muscles contracted chest raised and body held as tall as possible Exercises and practice in standing should be continued until the pain has subsided muscular strength has been improved and correct posture has become at least semiautomatic

The same exercises are used to advantage following heat and massage in the conservative management of the patient with a protruded disc in the lumbar region

In the treatment of back conditions it may be necessary to overcome certain basic deformities If the iliotibial bands are contracted the lateral fascia lata is stretched by the patient standing for a few minutes in the lame horse position with the hip thrust out toward the affected side while holding on to a suitable object Contractures of the anterior fascia lata are stretched by pulling backward on the ankle with the knee flexed in the prone position Contractures of the hamstrings are stretched by forward flexion of the trunk on the legs while sitting with the knees extended Short heel cords are relieved by standing with the forepart of the foot on a block and letting the heel drop below the level of the block so that the weight of the body is responsible for the stretching

It is to be remembered that poor functional capacity may be a contributory factor in backache even if other pathologic processes can be demonstrated Part of the pain in osteoarthritis of the spinal column, for example, may be the result of poor posture In such cases correction of posture alone often produces a surprising relief of symptoms Similarly, when operative procedures are performed to correct a defect of the spinal column they should be followed, when feasible, with corrective exercises and postural training

Fractures

Therapeutic exercise is the most important procedure in the physical treatment of fractures In the early treatment of fractures the use of passive motion is not advisable because the patient may contract his muscles to resist the motion, leading to possible displacement of the fragments

Active motion of all joints not necessarily immobilized should be insisted upon throughout the course of fixation to minimize muscle atrophy fibrosis, and limitation of motion From the first the patient should be instructed in exercises to maintain the function of the free joints and muscles

The primary exercises for the area involved by the fracture are muscle setting exercises to prevent loss of the sense of how the muscles act These should be performed 50–100 times daily until free action is allowed When there is sufficient union to permit temporary removal from the splints under manual protection, assistive active exercises should be started with the part supported to eliminate gravity There should be no forced movements as they lead to pain muscle spasm and loss of the confidence of the patient As soon as bony union is satisfactory, free active exercises should be started and continued until resistive exercises can be started and until normal strength and mobility has been re

gained This type of program is of considerable value in lessening duration of disability and amount of permanent disability following fractures

NEUROLOGIC DISEASES*

Hemiplegia

The hemiplegic state produced by cerebral vascular accidents is a condition often *seen in general practice* Exercises should be initiated early and continued until maximal return of function is assured Even if an initial complete flaccid paralysis is present passive exercises will help prevent the development of deformities The most common deformities to guard against are tightness of the shoulder leading to periarthritis, tightness of elbow, wrist, and finger flexors, and tightness of the heel cord A shoulder pulley is also of use in this program

As muscular function returns re education exercises should be instituted This is particularly important in the upper extremity for the abductors and flexors of the shoulder, and extensors of the elbow, wrist, fingers and thumb, which are usually weakest In the lower extremity, the primary aim is to strengthen the antigravity muscles and to overcome the hyperactive stretch reflexes which tend to keep the leg in extension Practice in walking, sometimes with a light dorsiflexion foot brace and a cane in the good hand is necessary Continued improvement may be noted for a *year or more with persistent re education* and walking exercises

Poliomyelitis

From the very onset of illness prevention of deformity is of prime importance A firm bed with *foot boards and properly* placed pillows minimizes deformities Passive exercises in which the parts are moved through as *full a range as pain permits* also aid in preventing such deformities It is often necessary to relieve tightness by stretching before much progress can be expected from other exercises Tightness is found *most frequently in the neck* back, shoulders, hamstrings, heel cords and quadriceps muscles

As soon as relief of pain and good range of motion have been attained, *co ordination of muscular action* is the next goal Muscle re education exercises are the important measures in this stage Ideally there should be a corresponding return of function of agonists and antagonists, so that muscular imbalance does not result Once muscular co-ordination has been obtained there is much less danger that deformities will develop

Efforts to increase muscular strength and to increase functional activity should then be begun *Progressive resistive exercises* are of value in this phase of strengthening particular groups of muscles Activities such as walking should be consistent with the patient s ability to perform them Braces and corsets are used when necessary to prevent faulty bodily mechanics These devices often can be discarded as strength increases

When it is apparent that no further improvement of function and activity of weakened muscles can be obtained training in *substitute muscular functions* must be considered This may well be after a period of a year or more Surgical treatment also may be necessary After surgical treatment the patient must be taught the proper use of tendon transplants or the proper use of extremities after other orthopedic procedures

Multiple Sclerosis

The problem of prescribing exercises for the patient with multiple sclerosis may be quite complex Usually there is a combination of spastic paresis in one or more extremities and some degree of ataxia Mus

* See also Chapters 20 and 21

cular re education and training in gait and balance are commonly employed in treatment Progressive resistive exercises help to strengthen weakened muscle groups Treatment of this type may preserve the patient s morale as well as prevent contractures and deformities The disease is usually progressive but there is always hope of a spontaneous remission which can be used to best advantage if maximal function has been maintained

Combined Sclerosis

In the combined sclerosis associated with pernicious anemia there is involvement of both the posterior and lateral columns The result of such a combination is a spastic type of weakness and a loss of sense of position The aims of exercises in this condition are the strengthening of weakened muscles, lessening of spasticity, and improvement of co ordination Active re education exercises and the use of Coulter s modification of the Frankel type of exercises form an essential part of treatment Changes in the spinal cord may not be entirely reversible by proper medical treatment so the disability due to residual changes must be corrected Months of treatment may be required before sufficient strength and co ordination are acquired to permit gait training

PERIPHERAL VASCULAR DISEASES*

Burger Allen exercises may be a useful adjunct in the treatment of peripheral vascular diseases These consist of the following positions The patient lies on his back with his legs resting on an inclined plane raised to an angle of 30–45 degrees for about two minutes then the patient sits with the legs hanging over the edge of the bed for three minutes while the ankles are dorsiflexed and plantarflexed, then inverted and everted and toes spread and closed Finally the patient lies horizontal for five minutes with the feet and legs wrapped in warm blankets

These exercises are repeated three to six times several times a day While there is no definite evidence that this procedure increases collateral circulation, it is assumed that it empties peripheral vessels and encourages circulation

Asthma and Emphysema*

Remedial exercises are advisable in all cases of asthma in which the attacks follow each other so closely that the overexpanding lungs do not have an opportunity to return to their normal size In such cases the thoracic muscles assume a new length and tone which tends to cause the chest to remain in the fully expanded position The lower part of the thorax remains fully expanded and diaphragmatic excursions are slight The important exercises in this condition consist of two parts

1 *Abdominal breathing* The patient lies supine with the knees drawn up and with one hand on the abdomen exhales slowly, first dropping the chest then the upper part of the abdomen, then with the chest fixed the patient relaxes the upper part of the abdomen and takes a short inspiration the exercise is repeated eight to sixteen times

2 *Side expansion breathing* The patient sits in a chair with a belt wrapped around the lower part of the chest or with the hands placed on the lower part of the chest as he exhales slowly first dropping the upper part of the thorax, then the lower part finally using the belt or hands to help expel the remaining air in the bases of the lungs The lower ribs are then expanded against the belt or the hands while the patient inhales slowly following which the patient relaxes the belt or the hands while exhaling then repeats the process

Initially asthma exercises may cause in

* See also Chapters 11 and 12

* See also Chapters 16 and 21

creased coughing or wheezing on full expiration However, this is *not an indication* for discontinuing the exercises A number of patients can abort impending attacks by these exercises This apparently is due to loosening and expulsion of mucus

Occupational Therapy

OCCUPATIONAL therapy is the logical link between physical therapy and return to ordinary working conditions Occupational therapy assists in strengthening muscles and increasing motion of involved joints as well as furnishing mental diversion for the patient To accomplish this occupational therapy should be prescribed by a physician as carefully as physical therapy The occupational therapist should be given exact directions concerning the motions that should be stressed and the amount of exercise the patient should undertake

One of the methods of increasing the range of motion of the hip knee and ankle is the use of a *bicycle jigsaw* The pedals on the saw may be adjusted to increase gradually the limits of motion of the joints Strengthening of the extensor muscles may be stressed by pushing the pedals or the feet may be strapped to the pedals and strengthening of the flexor muscles stressed by pedaling backward In the absence of a jigsaw, an ordinary bicycle with the rear wheels jacked up may be substituted When the ankle alone needs exercise, a *foot pedal saw* or *sewing machine* may be employed

Basket weaving or weaving on a frame raised to shoulder height is excellent exercise for the shoulders elbows, and upper portions of the back Planing or sawing in *carpentry work* will furnish good exercise for the shoulders and elbows A hammer with a built up handle to fit the hand with impaired grip may be utilized for wrist and finger exercises *Clay modeling* and *knot tying* are satisfactory for loosening stiff joints of the hand

Many of these activities can be carried out at home after the patient has been instructed by a trained occupational therapist Such activities because of their intrinsic interest often are followed longer than routine exercises and are of definite value if properly prescribed

Spa Therapy

THE Committee on American Health Resorts of the American Medical Association has defined a health resort as "an institution which gives major attention to the use of the special climatic and other natural therapeutic resources including mineral waters with which it is endowed by reason of its location Spas are health resorts built around mineral springs

Undoubtedly, American health resorts are not well known although it has been estimated that 40 000 to 50 000 and 12 000 to 15 000 patients take regular treatments annually at Hot Springs Arkansas and at Saratoga Springs Spa New York, respectively Many American physicians have been unfavorably impressed by the claims which have been made by certain spas The

advertisements for spas often written by laymen in the local chamber of commerce have all too frequently included exaggerated statements concerning the benefits available to patients irrespective of their diseases All too frequently the directors and personnel of American health resorts and spas cater to paying visitors rather than those who are ill Most of the large spas or health resorts in this country are owned by private corporations or individuals and in many spas the medical supervision has not been sufficiently emphasized One exception is Saratoga Springs New York, which is owned by the state The springs at Hot Springs National Park, Arkansas are controlled by the federal government although the water is distributed to many privately owned hotels and bathhouses The latter operate under regulations of the United States Department of the Interior

The value of spas has been known since the time of ancient Greece and Rome Hippocrates Aristotle, and Galen stressed the value of mineral waters In Rome public and private baths reached a high state of development Interest in spas as places for recreation and the treatment of disease later spread throughout Europe, Great Britain and America

Undoubtedly the recreational facilities of a spa have an important role in the treatment of patients The bulk of patients at spas have chronic illneses particularly cardiovascular rheumatic and gastrointestinal diseases Such patients are benefited by the chief advantage of a spa which is the removal of the patient from his every day responsibilities to an environment of rest and relaxation

Of course, mineral waters are considered to provide an essential part in treatment at spas They contain mainly alkaline and saline sulfates chlorides and bicarbonates Gases in the form of carbon dioxide hydrogen sulfide and radon may be dissolved in the water The drinking of these waters is stressed at many spas and detailed directions concerning the amount and times of administration are often given Many of these waters are diuretic and laxative in nature and have been recommended for these reasons However, no definite proof has been offered that these waters have specific value in the treatment of common cardiovascular, rheumatic, and gastrointestinal diseases

Hydrotherapy, in combination with massage and exercise is also an essential feature in spa treatment Certainly hydrotherapy is useful in the treatment of rheumatic conditions Many hospitals unfortunately do not have hydrotherapeutic facilities such as are available in spas The handling of the water from the springs is often complicated When hot springs are available, as for example in Hot Springs Arkansas an important problem is cooling of the water to temperatures which can be tolerated by the patient If hot springs are not available the water must be heated before therapeutic use Furthermore, in many spas an effort is made to retain as much as possible of the dissolved gases

After preparation the water may be used in a variety of ways It is commonly used in tubs or pools The tubs are usually over 6 feet long 2 feet wide and 2 feet deep so that the patient can be immersed completely The baths are often followed by massage and exercises usually given by locally trained masseurs or masseuses Very few spas have trained physical therapists who have had special instructions in the use of massage exercise, and other physical agents in the treatment of disease

The warm pools are of special value in the treatment of rheumatoid arthritis The warmth helps relieve muscular spasm and pain Most of the weight of the body is supported by the buoyancy of the water Arthritic patients can move their joints through the maximal arc of motion with a minimal amount of pain Active assistive

exercises can be easily given in such pools to improve the range of motion Such patients also may be able to walk in deep water when not able to do so without its help Pool therapy is also of considerable value in the treatment of the residual effects of poliomyelitis The buoyancy of the water can be utilized in exercising the weakened muscles Walking also may be made possible

Rehabilitation

PHYSICAL rehabilitation is that phase of medicine which follows diagnosis and specific treatment It is concerned with the return of the patient to the most nearly complete life compatible with his abilities and disabilities After a prolonged period of illness, reconditioning exercises will help him to regain normal strength and endurance in a minimum of time

In spite of the best medical and physical treatment, some patients are left with disabilities that may handicap them in their daily activities and their work It has been estimated that one in seven of the male working population in the United States is handicapped or disabled Too frequently such handicapped or disabled persons are not given sufficient physical or vocational rehabilitation to permit them to make the most of their abilities Ideally, such persons should have the ability to ambulate independently, to take care of their daily needs and to have some gainful occupation They should be taught to walk if possible, or at least to move about for short distances with mechanical devices They should be able to take care of their dressing and undressing feeding themselves cleaning their teeth, shaving telephoning writing and the many small tasks which are essential to normal living They may have to be retrained to entirely new occupations or shown how to adjust their handicaps to their previous occupations An extensive program may be needed to accomplish these aims

Regardless of what is to be done, the first step in rehabilitation is *evaluation* of the patient's physical disability, mental status, and previous vocational training The only way to evaluate the physical disability is actually to test the patient in certain activities Deaver and Brown have developed an objective scale to measure a variety of functions This scale serves as a measure of the initial disability and also of the patient s progress during retraining

Co-ordination of physical training with *psychologic retraining* is essential This is especially true if rehabilitation is started after a considerable interval of time has elapsed following the onset of the disease or injury During such an interval, the patient may have become dependent on other persons for even his simplest needs The patient must be taught to help himself No matter how intelligent or how well trained in a vocation he is, he is of little value to society or to himself if he cannot get to his place of work or care for his needs while at work As a general rule, fortunately, patients will participate in a rehabilitation program with considerable enthusiasm if the program is started as soon as possible after specific treatment has been ended Starting the program early also has the advantage of reducing the period of convalescence to a minimum

Not all patients can be expected to return to full employment Some will have to be employed in sheltered workshops

and a small percentage of patients will be able to work only in their homes However even many of the latter group of patients can be trained to become self supporting

The ideal development in rehabilitation has been the establishment of centers where handicapped patients can be taken after discharge from hospitals for a program of retraining Such programs are of definite value to society It has been shown that the earning power of 43 997 persons who underwent vocational rehabilitation increased from $6 510 556 to $77,786,696 This represents a return of forty seven dollars for every dollar invested in the program

More centers for physical medicine and rehabilitation and more people trained in this specialty are necessary before the large number of handicapped and disabled people can take their place in society as self respecting self supporting individuals

46. Therapeutic Radiology

J W J CARPENDER

IRRADIATION therapy by roentgen rays or radium should not be undertaken lightly or without proper consideration for other means of treatment Ionizing radiations of this type are always damaging and their effect is cumulative a fact which often is ignored by inexperienced persons In the following discussion emphasis is placed upon the choice of therapy that will affect *the best cure rate together with the best* functional result Another method of treatment that will provide equal curative bu poor functional result is regarded as secon choice In the majority of instances there i no choice in a few the choice is obvious The use of radium and roentgen irradiation for most benign conditions is unwarranted especially in those instances where other methods of management—althougł they may be slightly more arduous for both *physician and patient—are equally effi*cacious

Radioactive Isotopes

RADIOACTIVE isotopes in the control of disease are in a class with radium at the *present time They and the equipment* needed for their employment are expensive Their use requires special knowledge and equipment and for a considerable period of time will remain in the hands of those associated with large institutions It is doubtful if they ever will become part of the armamentarium of the general practitioner The dangers of the use of radioactive isotopes cannot be emphasized too *strongly Even where so-called tracer doses* are used caution must be employed and detailed calculations made to avoid irreparable damage to normal structures Physicians using these substances in therapy or *diagnoses must have the services of a phys*icist to avoid errors in dosage which might have serious effects on patients

*Malignancy of Female Genital Tract**

RADIUM and roentgen rays, alone or in combination, offer with few exceptions the best method of controlling malignancy of the female genital tract One of these exceptions is carcinoma of the vulva where damage to surrounding normal tissue outweighs the benefits of irradiation and radical surgery is the treatment of choice When carcinoma of the vagina exists the problem is quite different because surgery would almost certainly destroy all function which often can be preserved when intracavitary radium mold and external roentgen ray are used Lesions of the lower third of the vagina should be treated similarly to vulvar lesions

CERVIX

Where carcinoma involves the uterine cervix, the best treatment is irradiation Even in the hands of the most capable the results of surgery do not appear to be better than those obtained with irradiation There are several methods of irradiation which give comparable results The most widely accepted method entails the use of radium followed by external roentgen irradiation The addition of roentgen ray increases by about 15 per cent the number of five year survivals The usual methods employed consist of applying radium directly to the cervix in a container inserted into the vagina, and in a tube which is placed in the cervical canal and uterus

Recently the use of interstitial sources of radium has been advocated in the form of needles which are inserted into the cervix and surrounding tissues It is claimed that this method gives a better distribution of irradiation than do vaginal sources This is theoretically possible but in practice it is doubtful if an ideal arrangement of radium needles can be achieved Certainly the results have not been shown to be better, and the risk of infection and damage to other structures is greater

Replacement of radium treatment by roentgen ray irradiation using special applicators to direct the radiations to the cervix and fornices, has shown good results This is a special technic which requires familiarity with its limitations and hazards This treatment may prove to be the best method for carcinoma involving the cervical stump after incomplete hysterectomy Because this problem is difficult and the results of irradiation are poor, supracervical hysterectomy should not be performed when total hysterectomy is feasible

Brief mention should be made of adenocarcinoma of the cervix The usual lesion is a squamous cell type and many reports have appeared concerning the resistance of the glandular lesion to irradiation It is believed to be curable where adequate treatment is employed

Malignant Tumors During Pregnancy

A complication of special interest is a malignant tumor of the cervix which develops during pregnancy If the lesion is discovered early the routine treatment should be employed followed by termination of the pregnancy (if this does not occur spontaneously) or a malformed child may result When the lesion is discovered late in the pregnancy a caesarean section should be done as soon as the child is viable The uterus is not removed and routine treatment is instituted postoperatively as soon as possible If the lesion is discovered after labor has begun, forceps delivery is indicated if the carcinoma is small and a caesarean delivery if it is large, for with large

* See also Chapter 35

lesions there is great danger of fatal hemorrhage with vaginal delivery

UTERUS

In the United States, *carcinoma of the uterus* is considered to be best treated by a combination of irradiation and surgery Heymann of Stockholm has long been a lone dissenter to this approach and has designed small capsules containing radium with which the uterus is filled His excellent results are attracting more and more attention, and it may be that this method will be adopted as the best available At present, however, the usual treatment is administration of radium by inserting several sources into the cavity of the uterus, *followed by complete hysterectomy* in four to six weeks When surgery is contraindicated because of the condition of the patient or invasion by the tumor, external irradiation is employed It has been shown *that many formerly* inoperable tumors become operable following irradiation

OVARY

Carcinoma of the ovary is a surgical *problem, but in some cellular types* considerable relief by irradiation can be given the patient when abdominal metastases have occurred Dysgerminoma and granulosa cell tumors are often radiosensitive and pseudomucinous adenocarcinoma can be fairly readily palliated and some cures have been reported Krukenberg tumors give poor results

Urinary Tract

TUMORS of the urinary tract pose a number of special problems with considerable difference of opinion concerning the best methods to employ in their treatment With the exception of Wilms tumor, the treatment of adrenal, kidney, and ureteral *lesions is a problem for the surgeon* Not much hope of palliation can be offered by irradiation except in an occasional case In Wilms tumor preoperative irradiation produces the best results If the tumor has been removed, moderate doses of roentgen ray irradiation tend to increase the cure rate as the tumor is quite radiosensitive Inoperable tumors *are often made operable* by irradiation

There is considerable disagreement as to the best method of handling carcinoma of the *bladder* Many feel a cooperative effort by the surgeon and radiologist will eventually give the best results Some lesions are resectable because of location but where resection is not possible *irradiation* gives better results than other methods Control by *fulguration* is not justifiable because of the high proportion of recurrence, irradiation if adequately given, will control many cases It may be given by roentgen rays from multiple portals well directed and *localized, by contact roentgen ray therapy* through a cystotomy opening or by interstitial radium needles or radon seeds The method chosen must depend on the nature *of the lesion, the experience of the radiologist, and the materials* available Total cystectomy has become a rarely justifiable procedure as primary treatment

For carcinoma of the *prostate* orchiectomy and hormone therapy seem to be the best methods of treatment, but surgical intervention may be needed where obstruction occurs Palliation of painful bone lesions is often possible by roentgen ray therapy

Carcinoma of the *urethra* is less common

in women than in men In either sex the best results are obtained by irradiation Malignancy of the *penis* is also best treated in this way, mutilating operations do not offer any better results than may be obtained by interstitial radium and radium molds

The cure rate in some *testicular tumors* may be improved by proper use of roentgen rays following surgery Seminomas may be curable and 80 per cent five year survivals have been reported in early cases Choriocarcinoma, adenocarcinoma and teratomas do not respond to any lasting degree to treatment by combined surgery and roentgen ray Irradiation tends to prevent growth in the frequently affected abdominal and thoracic lymph nodes

Breast

CARCINOMA of the breast occurs most frequently in women, but when it occurs in the male breast it is an even more serious disease than in women Surgery is the preferred method of treatment, but there is difference of opinion as to the value of irradiation as an adjunct Some advocate preoperative as well as postoperative irradiation, others postoperative irradiation alone and still others prefer operation without any irradiation reserving irradiation for those cases that have distant metastases or for other reasons are deemed inoperable

Those who argue against irradiation claim that carcinocidal doses of irradiation cannot be given to the breast area and axilla without considerable skin damage Therefore they contend, adequate treatment is not given and surgery is responsible for the cures that are obtained Recent statistical evaluation of several series of cases tends to support this argument Other studies indicate that postoperative irradiation therapy increases the number of five year survivals by 5 to 8 per cent The method and thoroughness of the surgery may be responsible for this discrepancy as well as differences in methods of irradiation and in selection of patients The value of preoperative irradiation is even more difficult to establish Certainly it is of no value where disease is confined to the breast or has not escaped beyond the limits of the removable axillary nodes but where there is perinodal infiltration there is evidence to support its efficacy Perinodal infiltration cannot be determined before operation, so that if this form of treatment is to be used it must be given in all cases where there is clinical evidence of axillary involvement

Where adequate surgery is available and the lesions are operable according to the criteria of Haagenson and Stout, it is probable that irradiation is of no value When the quality of the available surgery is in question and the criteria of operability are less completely fulfilled, irradiation should be given both pre and postoperatively

Digestive Tract

IRRADIATION in carcinoma of the lower two thirds of the esophagus is merely palliative and radical surgery has more to offer In the upper one third irradiation sometimes is helpful

Carcinoma of the stomach small and large bowel, liver, gallbladder, pancreas etc are surgical problems and only rarely is palliation accomplished by irradiation This also applies to those tumors involving mesenteric or retroperitoneal tissues

When carcinoma of the anus is seen early and treated by interstitial radium, good results may be expected both as to function and cure, but where involvement is extensive, surgery is necessary, the exact procedure depending on the ability of the surgeon and the extent of the disease Colostomy with abdominoperineal removal of rectum and anus often is unavoidable

Lip

CARCINOMA of the lip may be treated adequately by radium, roentgen rays or surgery, the choice depending on the extent of the lesion and the cosmetic result desired In small lesions the cosmetic result usually is a little better when the treatment is irradiation, in moderate-sized lesions cosmetic results are equally good by either method, and in very large lesions the cosmetic result is best when skillful plastic surgery is performed

Tongue and Mouth

CARCINOMA of the tongue is best treated by roentgen rays or radium, with the choice depending on the location The difficulty of inserting radium or radon seeds into the posterior portion of the tongue and achieving proper distribution, makes roentgen ray irradiation a better medium here In the more accessible anterior two thirds of the tongue insertion of radium is preferred Surgery is undesirable because the results are no better and the effect of removal of portions of the tongue is detrimental to phonation

The buccal mucosa is another site where irradiation is the therapy of *choice Again* the facilities that are at hand and the experience of the radiologist should be the deciding factor in the choice between radium and roentgen ray When treatment is adequate the results of radium and roentgen ray irradiation are equally good Where the tumor arises in the mucosa over an alveolar process the problem is more difficult *Radium may be used* with fair success for small lesions because one can avoid bone damage, but recent developments indicate that for larger lesions involving the tonsils and pharynx external irradiation should be used, *although the* prognosis in pharyngeal lesions is very *poor In tonsillar lesions the results* are excellent

Nasopharyngeal Area

LESIONS of the *paranasal sinuses* require a combination of surgery and irradiation The most common treatment in this country consists of external irradiation followed by radium for recurrences Windeyer of London has advocated roentgen ray irradiation followed by radical surgery consisting of removal of the floor of the antrum and alveolus with later application of a radium mold if necessary His results are excellent and the method should receive widespread approval Ethmoid and sphenoid carcinoma are more difficult to handle and external irradiation probably is the best procedure unless the patient is willing to accept disfiguring surgery

Surgery is impractical in lesions of the *nasopharynx* and well planned roentgen ray treatment offers the greatest hope of cure Occasionally intracavitary radium therapy or the implantation of radon seeds may be of value

In mixed cell tumors of the *salivary glands* the results are poor and the lesions tend to recur Where the tumor is small and total removal is possible without facial nerve damage, surgery is indicated Large tumors seen late probably are best treated by roentgen rays but prognosis is poor These tumors are usually benign at first but may become malignant at any time

Larynx

Selecting the form of therapy to be used in malignant tumors of the *larynx* and associated structures is a difficult matter Lesions of the hypopharynx are best treated by external roentgen ray irradiation as are those of the supraglottic area In the former it is usually impossible to do complete surgical excision and in the latter more cures can be obtained by irradiation

When laryngeal malignancy is confined to the cord and the cord remains movable treatment should be by irradiation The prognosis is good and if there is a failure laryngectomy can be done Where the entire cord is involved and mobility is reduced but not lost, roentgen ray therapy still offers a fairly good chance of cure Total laryngectomy offers a slightly better cure rate but it can still be done if irradiation fails In making the choice one must take into consideration the age occupation and economic status of the patient If the voice is essential to the patient s occupation irradiation is preferred but if voice loss can be tolerated and it is essential that the patient resume gainful occupation as promptly as possible surgery is indicated Irradiation is the treatment of choice for poor surgical risks

Very extensive lesions should be treated by laryngectomy as should subglottic lesions which are not amenable to irradiation External roentgen ray irradiation is used in carcinoma of the larynx Radium except from an external source is of no value Bronchogenic carcinomas should not be irradiated except for palliation

Nervous System

THE treatment of tumors of the central and peripheral nervous system is primarily surgical. Malignancy arising from nervous tissue, with few exceptions, is resistant to radiation. In the case of the rare sensitive tumors such as medulloblastoma, special technics may give a five year survival rate of over 50 per cent. The entire brain and spinal axis must be treated as a single unit. Despite poor success in other types of tumors it is the usual practice to irradiate where the surgeon is unable to remove the entire lesion.

Retinoblastoma presents a difficult problem. The lesions are moderately radiosensitive but the treatment of choice where only one eye is involved is surgical removal. Postoperative roentgen therapy is given where pathologic examination shows extension to the nerve stump. Involvement of both eyes is found in 50 per cent of cases either when first seen or at a later date. Roentgen irradiation is usually selected for the treatment of the second eye or for the eye showing least involvement where both are involved when the patient is first seen. The method of application to save the sight in the treated eye is highly specialized. *Neuroblastomas* vary in their sensitivity to radiation. The treatment is primarily surgical.

Pituitary Gland

LESIONS involving the pituitary gland fall in a special category. Good results are obtained in eosinophilic tumors where the progress of acromegaly can be arrested in many cases. In basophilic tumors cure is occasionally obtained and a fair number of patients will show arrest of Cushing's syndrome. Before irradiation is given in this condition adrenal tumor must be ruled out. Chromophobe adenomas are considered resistant but clinical improvement often results.

In all pituitary tumors great care must be taken in administering roentgen rays and frequent determination of visual fields must be made. Where the tumor is large one should be prepared to do emergency decompression to save rapidly diminishing vision. Rathke pouch tumors are radioresistant and are a surgical problem. Except in occasional Ewing's tumors malignant tumors of bone should not be irradiated except for palliation of inoperable cases.

Skin

NO DISCUSSION of the multitude of benign skin conditions will be undertaken. These fall in the province of the dermatologist.* However irradiation should not be used wherever comparable results can be obtained by other methods of treatment. Recurrent conditions such as psoriasis should never receive irradiation.

Malignant skin disease is a problem shared by the radiologist and dermatologist. Either radium or roentgen rays may be used with the quality of the radiation depending on the location and extent of

* See Chapter 38

the lesions Small superficial, squamous, or basal cell carcinomas may be treated by contact or superficial roentgen ray therapy Lesions over bony prominences or cartil age or very large lesions, or those in the neighborhood of the orbit often are best handled by radium molds or plaques or interstitial needles may be chosen One exception is malignant melanoma which is among the most radioresistant of malignant tumors Occasional metastases may be pal liated by radiation, but the problem is primarily one for radical surgery

Metastases

EXCELLENT palliative results have oc curred following irradiation therapy of metastases from many types of lesions The relief of bone pain in metastases from pros tate and breast tumors is often spectacular and it is possible that a cure may be ob tained by the irradiation of a solitary metastasis from a sensitive tumor Except where only one or two metastases are pres ent a curative dose should not be attempted Symptomatic relief governs the amount of radiation to be given

*Thyroid Gland**

DISEASE of the thyroid gland, while largely a surgical and medical problem is occasionally of interest to the radiologist For many years, inoperable cases of hyper thyroidism uncontrolled by medical means have been treated with roentgen ray irra diation This has been largely supplanted by the use of radioactive iodine or propyl thiouracil Radioiodine now obtained from the Atomic Energy Commission in the form of a solution of the isotope I^{131}, emits weak beta particles and gamma photons as it decays with a half life of eight days Its metabolism is the same as that of normal iodine It is almost entirely collected in the functioning thyroid gland where it irradiates the tissues Excellent results have been obtained but it should not be used where surgery is possible

Radioactive iodine, I^{131}, is used in carci noma of the thyroid but the results are not as good as in hyperthyroidism Unfor tunately, uptake of iodine by malignant thyroid tissue is largely dependent upon the degree of differentiation present and as the tumor departs from the normal gland structure the assimilation of iodine becomes less It has been possible to en hance the utilization of iodine by tumor and metastases by removal of all normal thyroid tissue and by the use of thyroid stimulating hormone It appears that the tumor tissue attempts to take over the function of the missing normal tissue When enough iodine is utilized by the tumor to give adequate levels of irradia tion, results have been excellent In malignancies showing insufficient uptake, palliative roentgen ray and radium therapy is the only choice where surgical removal is impossible Wherever complete surgical removal is possible, it is the treatment of choice

* See also Chapter 29

Blood

HODGKIN S disease lymphosarcoma reticulum cell sarcoma and the chronic leukemias may be considered as a group They are all radiosensitive and for years the best method of treatment has been roentgen ray irradiation Urethane ACTH cortisone and nitrogen mustards have altered this therapeutic approach somewhat

In the chronic leukemias P^{32} radioactive phosphorus is a useful substance Frequently roentgen ray irradiation must be used to reduce large lymph nodes or spleen but the radioactive phosphorus with a half life of fourteen days bears the brunt of the therapy With its use radiation is largely limited to the bone marrow The results with respect to prolongation of life are no better than when roentgen rays are used but the absence of radiation sickness makes the treatment desirable

In Hodgkin s disease and occasionally in the lymphosarcomas and reticulum cell sarcomas nitrogen mustard gives excellent remissions Used in conjunction with roentgen ray therapy this substance will prolong life for many years It is best used for generalized disease with roentgen ray being used for limited local involvement and with alternation of the two methods when the condition appears resistant to one or the other Other newer chemotherapeutic approaches are now under study

Other radioactive isotopes have been tried in treating these conditions radioarsenic radiosodium radiomanganese and radiogold being the most widely used Their effect is similar to total body irradiation because they fail to localize in any one organ or tissue With the exception of radiosodium which is employed for diagnosis of vascular disease, their use is still largely experimental

Other Uses

IRRADIATION therapy is employed to good advantage in certain benign conditions Polycythemia vera has long been treated by roentgen ray therapy but this has now been supplanted by radioactive phosphorus except in those cases easily controlled by occasional phlebotomy Although it is considered to be the treatment of choice the dangers of indiscriminate use of radiation should be emphasized Painful herpes zoster is often relieved by roentgen ray therapy administered to the spinal roots Treatment should be given early because the results become poorer as time elapses Before the advent of modern chemotherapy furuncles and carbuncles were often treated by roentgen ray The results are good and chronic axillary furunculosis is still often referred to the radiologist

A thorough review of the literature will reveal few if any conditions that have not been subjected to irradiation therapy It has been claimed that irradiation is the treatment of choice in chronic arthritis subacromial bursitis asthma rheumatic heart disease benign giant cell tumor, and numerous other conditions but the claim is false These diseases may be treated in a variety of ways and the results of irradiation therapy are no more spectacular or advantageous than those from other methods of management In many of the condi

tions for which irradiation has been advocated, the results can hardly be evaluated because of the high percentage of spontaneous remissions Recently a large series of patients suffering with gastric or duodenal ulcer have been subjected to roentgen ray therapy in the hope that the radiation would produce suppression of acid secretion Suppression of secretion does occur, but this is frequently a transitory effect In view of the danger of using radiations, one cannot recommend this therapy as a substitute for adequate medical management even though the latter requires considerably more effort on the part of the clinician

A word of caution is needed concerning the treatment of hypertrophic lymphoid tissue in the nasopharynx at the orifice of the eustachian tube There is in widespread use at present a lightly filtered radium applicator which delivers a very high dose of beta radiation to a small field in a short period of time The late effects of this treatment are not known, and until they are known the treatment should not be given unless the need is clearly evident

47. Diagnostic Radiology

RUSSELL L. NICHOLS

THE roentgenographic examination of a patient is one of the most frequently employed clinical diagnostic aids As with other commonly used but highly specialized procedures, abuses are frequent In many instances lack of understanding of the basic physical principles governing conduct of such examination has led well meaning physicians to employ procedures that were either useless or detrimental to the patient Failure to recognize the importance of various anatomic and physiologic factors has resulted in abuses both in the making and interpreting of roentgenograms Inadequate liaison between the radiologist and the clinician in charge of the case has all too frequently been the cause of misunderstandings which were costly

From time to time the radiologist is asked to 'rule out this or that lesion In many instances, such a feat is impossible In such cases mutual understanding by radiologist and clinician of the basic limitations inherent in the examination is a necessity The written report cannot always clarify these limitations Thus, personal consultation must fill the gaps which the written report may fail to bridge The purpose of this chapter is to cite specific examples which most radiologists believe are abuses of good practice and to outline certain limitations in the routine reporting of films which those who use the reports must recognize

Physical Limitations

ALL roentgenographic diagnosis is based on the relative roentgen ray opaqueness of air fat, water, metal salts within the body, and opaque contrast materials introduced into the body The clinical value of the roentgen examination depends on ability to record the contrast due to these different degrees of opacity on film or to see them on the fluoroscopic screen Certain physical phenomena limit ability to record contrast As a roentgen ray beam passes through the body, three things occur Part of the beam which enters the body is completely absorbed, part of the beam penetrates the body without change, and part of the beam is scattered The scattering which occurs resembles the effect visible when a beam of light passes through a cloudy emulsion

A solid object suspended in such a cloudy emulsion will still cast a shadow but the contrast at the shadow margin will be reduced by the scattered light which the surrounding milky medium produces In the same manner, the scattered portion of the beam reduces contrast between details of the part being examined and thus limits ability to recognize these details

The radiologist has means at hand for reducing the effect of such scattered radiation, such as voltage control the use of the parallel leaf grid, limitation of beam size, and modification of position of the patient However, as the thickness of the part examined increases the amount of scatter radiation increases thus reducing ability to record or appreciate minimal degrees of contrast The fact that minimal contrast is increasingly difficult to appreciate at lower levels of illumination makes this factor of scatter radiation important in fluoroscopy

Increasing thickness of the part examined also increases the proportion of the beam which is absorbed by the body Up to a certain point this fact is of little importance because the brightness' of the incident roentgen ray beam is merely increased so that the optimum intensity of the emergent beam is maintained However, in thicker parts of the body mechanical and electrical limitations force either an increase of the exposure time in filming or acceptance of the dim image of the fluoroscopic screen Increasing exposure time almost invariably means increasing lack of definition of the image due to motion of or within the part being examined This factor of motion during the time of exposure becomes increasingly important in patients where cooperation is a problem Thus examination of infants, senile patients, and patients with whom language offers a barrier are usually more difficult to control and the final report more open to question than in the average adult

Chest

ROENTGENOGRAMS of the chest are routinely made with exposures which range from $\frac{1}{10}$ to $\frac{1}{60}$ second While even at these speeds a small amount of unsharpness due to motion must be tolerated, most motion is frozen However, with portable apparatus chest filming requires from $\frac{1}{4}$ to 1 second in other words during the time of *exposure the heart can complete almost* one full cycle Similar exposure times are required by most microfilming apparatus The consequent lack of sharpness due to motion within the chest during exposure must be accepted and the relative lack of certainty of the final report understood

It should also be noted that portable films of chest are most frequently requested in patients who are extremely ill frequently unable to cooperate, and often too dyspneic to be able to suspend respiration during the time of exposure In such instances the bedside unit examination offers little more than blurred confusion for any pathologic process less than 2–3 cm in diameter The position of the patient at the time of filming must also be considered—for example, *fluid air levels are ordinarily quite easy* to see in the routine examination when they are made with the patient upright and the central roentgen ray beam directed parallel to the floor However, such a fluidair level becomes almost impossible to establish when the patient is supine and the central ray perpendicular to the floor, as is frequently necessary with bedside filming

From time to time inquiry is made con

cerning the lower limit of size of a lung lesion visible by roentgen ray examination An average screen film combination will define minute patterns of 10 line per mm However other factors leading to unsharp ness prevent utilization of detail at this fine degree of resolution When multiple lesions are present throughout the lung fields, as in miliary tuberculosis, they prob ably can be seen only after they have reached 1–2 mm diameter The recognition of a single lesion in the lung field is more difficult than the recognition of multiple scattered densities Ordinarily a single lesion, such as a tuberculous infiltrate, must reach about 5 mm diameter before it can be distinguished from normal surrounding structures While microfilming technic suf fers from several additional sources of un sharpness, the lower limit of size of a recognizable solitary lesion in the lung field approaches that recognizable in a film of standard size

In addition to the size of a given lesion there are several other factors which must be kept in mind when chest films are viewed There is a considerable amount of lung tissue hidden behind the diaphragm and behind the heart in the routine frontal view It is true that good films permit visualization of some of the retrocardiac lung structure and that lateral views can project this portion of the lung clear of the diaphragm and the heart However lateral views suffer from the unavoidable handicap of piling up of structures because of the greater depth and, consequently shadow outlines are more confusing and our ability to see lesions in these areas of lung remains more limited than in the remaining clear areas The overlying soft tissue shadows of a heavy breast occasionally limit visibility in the lower lung fields and costophrenic angles Occasionally confusion may arise in distinguishing normal lung structure from pathologic process—for example the piling up of normal bronchovascular markings may imitate a pulmonary cavity If the chest has been examined without stereo scopic views, confusion may arise from an overlying hair braid or a bulky lesion on the skin over the lung fields, such as a hemangioma, or from a pleural density, any one of which may imitate a lesion within the parenchyma of the lung

DIAGNOSIS

Once a lesion has been found and studied, the problem of etiology must be considered At this point one must note the nature of the evidence available on the roentgenogram which can lead to an etiologic diagnosis or which may simply prove misleading An indistinct margin of a zone of airless lung in the apex or sub apex is most often due to tuberculosis, yet there are occasions when virus pneumonitis may present an identical appearance The roentgenogram depicts only the size, shape, position and density of the lesion, and these characteristics, as well as the gross appear ance of a zone of tuberculous pneumonitis is quite similar to that of a zone of pneu monitis of virus etiology Thus, the two lesions may be indistinguishable at a single roentgenographic examination The diag nostic problem that arises when one is con fronted with multiple tiny nodules scattered throughout both lung fields presents an excellent example of the complexities of dif ferential diagnosis involved in the inter pretation of a lesion that appears relatively simple Such an appearance may be due to one of the dust diseases of the lung, such as silicosis, asbestosis or beryllium granulo matosis Boeck's sarcoid may produce an appearance indistinguishable from these clinical entities Occasionally a chemical pneumonia may produce a nodular appear ance throughout both lung fields Miliary tuberculosis bronchomycosis due to such organisms as *Monilia*, *Aspergillus* and *Coccidioides immitis* may also produce an appearance indistinguishable from the

others The passive congestion of cardiovascular disease and miliary carcinomatosis likewise may produce such an appearance Endless examples could be cited of either difficult or impossible differential diagnoses of lung conditions but the one important feature to be emphasized is the abuse of good medical practice that occurs when the roentgenogram is considered alone without due regard to the clinical condition of the patient

Tuberculosis*

The problem of attempting to distinguish between active and inactive tuberculous lesions is occasionally quite difficult Little doubt concerning activity can exist when an obvious cavity and surrounding dense lung tissue are present Criteria such as extent of calcification shape and density of the lesion (particularly when compared with previous examinations) and degree of reaction of surrounding tissues frequently guide decisions in the more difficult cases However when there is an opportunity to view microscopic sections of a lesion that appeared densely calcified on the roentgenogram one frequently finds the calcified areas interspersed with caseous tissue and occasionally with minute zones of activity

* See also Chapter 16

at the periphery of the lesion When t diagnostician is confronted with the pr lem of judging the activity of a tubercul lesion after collapse therapy, either thoracoplasty or paraffin pack, he loses e the usual criteria In such instances e the technic of using roentgen rays must adjusted to fit the clinical problem

Infant Chests

The interpretation of roentgenograms chests of infants particularly of newbo infants is surrounded by numerous falls Here one must remember that film is seldom accomplished at the height inspiration and is more frequently done the mid phase of expiration Slight degr of obliquity at the time of filming all frequently cause an appearance which tates that seen with a lesion in the l field or they present a peculiar appeara of the outline of the heart which may interpreted as evidence for congen cardiac abnormality The shadow cast the thymus in the newborn infant has b the subject of many recent errors of in pretation This shadow may occupy alm the entire upper lung fields and still within normal limits of weight, size a shape

Heart

RECENT advances in surgery of the great vessels has increased the importance of accurate diagnosis of congenital cardiac lesions Of late there has been such emphasis on the subject of *angiocardiography* that one is likely to forget the important information that can be gathered from routine films of the chest and from fluoroscopy of the heart At fluoroscopy one can ordinarily obtain a fairly good idea of the size of the several cardiac chambers Nu ous methods have been presented for termination of the size of the card silhouette However too rigid interpre tion of this estimate of cardiac size is warranted We have found many instan in which cardiac size has varied to 15 cent above and to 10 per cent bel average in which the heart was fou entirely normal at autopsy

Angiocardiography is not to be under taken lightly While angiograms of a sort can be made with routine apparatus, a formidable procedure of this sort is much better carried out when special *filming* apparatus capable of making films at no less than one per second is available

Digestive Tract

PHARYNX AND ESOPHAGUS

Physical examination of the pharynx and hypopharynx, particularly relative to the mechanism of deglutition, presents many difficulties However, roentgenographic ex amination of this area presents even greater difficulties The area must be examined by noting the contrast of the air column against the soft tissues, by introducing opaque medium or by a combination of both The contrast presented by the air when seen against the soft tissue is relatively poor and the abnormalities which may be distinguished by this method are relatively gross

When an opaque material such as barium suspension, is introduced into pharynx and hypopharynx the act of swal lowing carries it out of the field with great rapidity, scarcely allowing time to observe the shadow fluoroscopically and presenting considerable difficulty in obtaining films of the area One other factor adds to the diffi culties—the relatively large size of the pharyngeal passage and its normally irreg ular outline While gross abnormalities of the mechanism of deglutition and of the anatomy of the hypopharynx are evident at the roentgen examination, it should be remembered that roentgenographic exam ination of this area ordinarily adds little to good physical examination and is much more often a superfluous medical luxury *rather than sound diagnostic procedure*

Esophagus

After barium passes the hypopharynx and enters the esophagus an entirely dif ferent situation occurs Here the relative ease of roentgen ray examination compared to physical endoscopy represents a decided advantage Visualization of the esophagus through the air *containing lung fields* presents a minimum of technical difficulty The narrow lumen of the esophagus pre sents vision of lesions of relatively small size While such lesions as neoplasm, benign ulcer, and diverticula are relatively easy to see, there are others that may not present positive roentgenographic findings Many esophageal foreign bodies are thin and platelike in structure and frequently in visible in certain projections They may cause little or no deformity of the esopha geal outline and no disturbance of the progress of the liquid barium column dur ing the course of swallowing In such in stances one may be aided by watching the progress of a barium gelatin bougie as it progresses down the esophagus However even when this precaution is observed the lack of roentgenographic evidence of an esophageal foreign body does not "rule out its presence Small varices in the lower por tion of the esophagus are occasionally dif ficult to distinguish from air bubbles Un doubtedly a certain proportion of these lesions goes unrecognized and in other instances diagnosis can be made only after repeated visualization of these tiny ab normalities In early scleroderma of the esophagus, a *physiologic disturbance of the* progress of peristalsis may be the only visible abnormality, there being no demon strable variation in the mucosal pattern or the shape of the esophagus However, the

significance of such physiologic disturbance may often be open to question and in some instances can be held significant only after it has been visualized at successive examinations

Hiatus Hernia During the last ten years the significance of the clinical syndrome associated with hiatus hernia has become more generally known and the roentgen diagnosis of this lesion more frequently made However here again it should be noted that a negative report must be open to question There are occasions when such a lesion is present only intermittently and at the time of examination it may be impossible to produce the typical roentgenographic appearance There are other instances where gastric mucosa is present above the level of the diaphragm arranged in longitudinal folds so as to perfectly imitate the mucosal pattern of the lower esophagus In such instances a true hiatus hernia may be present and repeatedly go unnoticed by the radiologist

STOMACH

The normal variations in size, shape and position of the stomach are so numerous that they defy adequate description in words There was a period in the early days of roentgenographic examination of the stomach when it was fashionable to pay great heed to the position of that organ within the peritoneal cavity It is unfortunate that most of us must have our anatomic training by dissecting fixed cadaver specimen as we picture in our minds the appearance of a shrunken stomach high in the left upper quadrant of the abdomen This picture is far from reality and it has taken physicians many years to learn that the body of the stomach may enter the true pelvis and still be in no way abnormal We still occasionally hear of the diagnosis of gastroptosis and of various means of treatment of this pathologic ghost

An interesting problem is presented each time ulcer of the stomach is found The differentiation between benign and malignant ulcer sometimes is easy, usually difficult, and occasionally impossible Numerous differential signs have been established and, while many of these are reasonably dependable, none is infallible

The term pylorospasm is used freely by some radiologists to describe the physiologic state of the prepyloric antrum and pylorus which leads to slow filling of duodenum, yet stomach and duodenum fail to show intrinsic deformity or crater While such a physiologic state may be the result of unseen pathology in the region, an identical appearance may result from remote causes such as mental tension associated with the strange surroundings at the time of examination

Examination of the stomach after surgery presents special technical difficulties and these difficulties are increased when the radiologist is not informed in advance that surgery has been done Forewarned of surgical anastomosis between stomach and loop of small bowel the examiner proceeds carefully, attempting to avoid flooding of the field before the mucosal pattern has been studied in detail In spite of all precautions, however the mucosal pattern in the region of the anastomosis frequently is complex and confusing and it is occasionally difficult to establish the presence of ulcer at the margin of such an anastomosis

DUODENUM

In many of the lesions of the stomach, gastroscopy provides a means of confirming or challenging the roentgenographic diagnosis and if surgery is done there is an even more conclusive check on its validity In the case of the duodenum however, the radiologist works almost alone His situation is unfortunate and can be compensated for only by rigorous analysis of the data and constant self criticism Formerly, the diagnosis of duodenal ulcer was based almost

entirely on the secondary effects of the ulcer —*in other* words either the active de formity of the bulb or the scarred sequelae of the ulcer However in *the light* of present knowledge one should not be con tent with such diagnosis An ulcer crater may exist in a duodenal bulb without significant deformity and on the other hand extreme deformity of the bulb may be present *without* an active crater—the two must be distinguished and the crater visualized before the diagnosis of active ulcer can be made In some duodenal bulbs this proves to be a simple problem but sometimes the anatomic *disposition of the* organ is unfavorable and it is difficult to obtain a good view of the duodenum This is particularly true in stocky persons where the bulb may be adequately visible only in the extreme lateral position In this posi tion the fluoroscopic image is dim and even craters as large as 3 to 5 mm may go un recognized Undoubtedly small craters in undeformed bulbs frequently go undiag nosed in such subjects

PROXIMAL PORTIONS OF SMALL INTESTINE

After barium leaves the duodenum con tinuity of observation is lost patterns be come complex and overlapping the barium stream discontinuous and even if fluoros copy is continued so long as to endanger the health of both patient and observer it is almost always impossible to trace the entire course of the small intestine Isolated lesions *sometimes are detectable* partic ularly when they produce partial obstruc tion but only those conditions that involve large segments are regularly demonstrable Administration of barium through a Miller Abbott tube sometimes is helpful but regardless of the methods employed isolated nonobstructive lesions such *as diverticula* polyps or neoplasm are apt to be missed *In the present state of the* art the radi ologist s report of ' normal small bowel study cannot safely be interpreted as mean ing more than this no demonstrable stage of generalized lesion of the small intestine is present no obstructing lesion is present and no isolated nonobstructing lesion has been found

TERMINAL ILEUM

The situation is quite different in the case of *terminal* segment of ileum, *which is* best examined in connection with a barium enema study However, the reflux filling of ileum from the cecum frequently requires skill and perseverance on the part of the examiner and sometimes considerable forti [illegible] on the part of the patient When it [illegible] demonstrated on film stud[illegible] lesions of tuberculosis or regional enteritis are readily detected by this type of exam ination In that troublesome but fortun ately small number of cases in which reflux filling does not occur, the only recourse is fluoroscopy and filming following oral barium In these instances *study of termi nal ileum* particularly of its *mucosal* pat tern is seldom as adequate as that accom plished by barium enema

COLON

The technic of *examining* the *colon by barium* enema is fairly well standardized and both fluoroscopy and *film studies* are *employed The loops of the rectosigmoid* the obliquely placed *hepatic and* splenic flexures and the *irregular* position *of* the cecum are seldom well seen *on* standard film views and can *be adequately examined* only when the *radiologist can* view and move the patient *at* the same *time* Visual *ization of the sigmoid colon* presents the greatest *problem* Here *the several* loops *frequently* form *confluent* patterns which may be *only* partially uncoiled when the patient is placed in the extreme *lateral position* In such a position the fluoros

copist must observe the intestine through the greatest lateral thickness of the body At this point the fluoroscopic image becomes so dim that even a lesion of major size may be overlooked

In any examination where a lesion of the rectosigmoid colon is specifically suspected the omission of films made in oblique and lateral positions or the omission of proctoscopy represent an abuse of good practice which may cost the physician the possibility of making the correct diagnosis and may jeopardize the patient s life Visualization of the cecum is ordinarily quite simple However, in those instances where neither appendix nor terminal ileum can be visualized the identification of the cecum becomes extremely difficult and one must keep constantly in mind the possibility of a gross obstructing lesion which is preventing their visualization

The presence of small polyps within the colon presents a special radiologic problem Small polyps may frequently go unseen through the rather thick barium column which fills the colon and often become confused with the mucosal pattern in the postevacuation views Small fecal masses may imitate perfectly a small polyp The earch for polyps in the colon requires a ainstaking time consuming examination ten with special film views and possibly th special barium mixtures Thus an mination for their detection should not ntered upon lightly

ne examination of cases of chronic pecific ulcerative colitis frequently ts confusing situations This is due fact that the radiologist s criteria for is concern themselves with the y effects of the disease The stif ortened tubelike colon that the t visualizes is the result of scar bmucosa and muscularis and of

the disruption of the normal neuromu pattern The early stages of this d may be represented only by relatively s ficial changes in the mucosa and thus infrequently limited only to the most d cult portion of the colon to visualize rectosigmoid Thus in early stages of th disease the symptomatology and procto scopic appearance may be quite typical yet the radiologist finds only a normal appearing colon In later quiescent stages of the disease the radiologist may find the typical picture of ulcerative colitis and the patient be completely symptom free

APPENDIX

Seldom if ever can the radiologist be of aid in the diagnosis of disease confined to the appendix It is obvious that the local manipulation and distention of cecum required for barium enema must be avoided when acute appendicitis is suspected Many roentgenographic signs of chronic appendicitis have been described Retention of barium within the appendix is a normal phenomenon Segmentation of the barium column within the appendix is ordinarily due to fecal masses which share the limited lumen with masses of the opaque material Neither retention nor segmentation of barium by the appendix has any relationship to disease At most these signs reveal that the lumen of the appendix is patent At fluoroscopy the appendix may be found fixed in one position While such a condition is seldom a normal anatomic variant and is most frequently the late result of inflammation it does not follow that appendical adhesions are producing symptoms Tenderness in the area of appendix noted at fluoroscopy must also be interpreted with caution This sign is subjective and bears no consistent relationship to the state of the appendix.

Gallbladder

USEFUL application and adequate interpretation of cholecystograms depend on the knowledge of gallbladder physiology Visualization of the gallbladder is dependent on at least four separate steps—first, the absorption of the contrast material from the gastrointestinal tract second the excretion of the contrast material from the circulating blood into the biliary tree, third, the entry of the contrast containing bile into the gallbladder, and fourth, the concentration of this bile by the wall of the gallbladder Interruption of any one of these steps may result in nonvisualization of the gallbladder Thus, in the presence of impaired liver function the report of nonvisualization of the gallbladder must be taken as meaning that insufficient amount of the contrast material has reached the gallbladder to be concentrated into a visible shadow It should not be assumed that the gallbladder is unable to concentrate the substance The application of cholecystography too soon after acute cholecystitis frequently results in nonvisualization of the gallbladder, which recovers its ability to concentrate bile rather slowly, ordinarily not before two or three weeks have passed after inflammation

In many institutions standard examination of the gallbladder requires roentgenograms after administration of some preparation calculated to cause the gallbladder to contract While such postcontraction views of the gallbladder may occasionally provide useful information, too strict interpretation of the presence, absence or degree of contraction is not warranted Gallbladder emptying is a complex phenomenon controlled by several diverse mechanisms The diagnosis of gallbladder disease based on the criterion that the gallbladder has failed to contract or that it has contracted too sluggishly is frequently in error

Skeleton

SKULL

The examination of the acutely injured patient presents numerous difficulties for the radiologist particularly in the case of head injuries do these difficulties become of such great degree as to make the final value of the examination questionable Adequate examination of the skull requires considerable cooperation from the patient to assume and maintain the several positions which are necessary in the examination It is distressing to watch the difficulty encountered when routine skull views are attempted on a disoriented and frequently agitated patient who has recently suffered injury to the head Such a patient is ordinarily in need of treatment for shock and for his brain injury rather than examination of the bony case for the brain Roentgenographic examination at this time may add to the patient s already critical injury

The interpretation of skull films in cases of suspected bony injury is ordinarily a relatively simple problem However, fractures not infrequently occur in the base of the skull where visualization on routine views is extremely difficult Even after the patient has recovered to sufficient degree to obtain adequate views of the base of the skull these may fail to present evidence

of abnormality even though excellent clinical evidence may indicate the presence of a fracture in the base

AXIAL SKELETON

Adequate examination of the axial skeleton is, under most circumstances a simple procedure Even in the injured patient, adequate views for diagnosis of the degree of bony injury ordinarily are easily obtained However there are two areas where visualization is difficult in the region of the first cervical vertebra and at the cervicothoracic juncture Visualization of the atlanto occipital articulation, except by laminography, is a rare feat even in a normal patient Visualization of the dens of the second cervical vertebra and the relations of atlas and axis frequently are quite difficult, particularly in the injured However, there are many instances where information concerning this area is of such paramount importance that examination and interpretation must be attempted Fair lateral views of the cervicothoracic juncture can be obtained in the uninjured patient, but if the question of fracture arises the patient is not able to cooperate in obtaining these views Consequently, dependence must be placed on views taken in supine or oblique positions thus making the interpretation of fracture more difficult and the possibility of missing fractures of small degree greater

BONES

The problem of the early diagnosis of acute hematogenous osteomyelitis has always been difficult Ordinarily roentgen signs of such lesion do not appear until several days after the acute onset of symptoms Certainly the beginning of treatment of this disease should in no instance wait upon roentgen ray diagnosis

Occasionally confusion occurs in distinguishing tumor from osteomyelitis The advent of the sulfonamide drugs and the antibiotics have made instances of this confusion more frequent After the administration of such drugs a smoldering infection in bone may destroy its continuity in bizarre fashion The resulting appearance of bone destruction and periosteal new bone may strongly imitate the appearance seen in malignant neoplasm Thus, the final diagnosis of such lesions should rest with biopsy Radiologists not infrequently have attempted to distinguish between the several types of bone tumors While each of these tumors does present certain characteristic radiologic patterns, none is sufficiently definitive for exacting diagnosis Thus the patterns of periosteal new bone, the sun ray formation frequently associated with Ewing s sarcoma, may be similar to those of osteogenic sarcoma Histologic definition of tumor type rests with the pathologist

Kidneys and Ureters

INVESTIGATION of the structure of the renal tract by means of intravenously introduced contrast material has become a valuable and more or less routine procedure Limited information relative to the function of the kidneys may be obtained from this examination However, poor visualization of the calyceal and pelvic system does not necessarily mean impaired renal function Systemic reaction to the intravenous introduction of the contrast material may temporarily impair renal function to a degree where the kidneys are not visualized Instances probably occur where

the patient's marked volume excretion at the time of the examination produces only faint visualization of the structures in question

Unfortunately, the fine structure of the kidney is occasionally obscured by overlying gas Routine attempt to rid the patient of such abdominal gas is of value but by no means always successful Interpretation of the sketchy visualization which results when these overlying gas shadows are in the way must be approached with the utmost caution

Female Genital Tract

ROENTGENOGRAPHIC examination of the cavity of the uterus and fallopian tubes is a fairly simple means of obtaining valuable information in sterility problems The opaque medium, usually iodized oil must be injected into the uterus under controlled pressure The use of makeshift apparatus which does not permit measurement and control of the pressure applied is to be condemned Salpingography may reveal small filling defects within the oil column filling the uterine cavity While such a filling defect may represent a mural polyp redundant folds of the uterine mucosa depressed by the uterine cannula or even air bubbles may present a similar appearance When a patient is being examined by this means for the second time care must be taken to observe the amount of oily contrast material remaining from the original examination Iodized oil may be seen smeared over the pelvic peritoneal surfaces for eight to ten months after the first examination Diagnosis of patency of the fallopian tubes at repeat examination should be made after due evaluation of the amount of contrast material remaining from the original examination

Roentgen pelvimetry can provide valuable information concerning size and con figuration of the birth canal However meticulous attention to technic and special adaptation of apparatus is necessary Once reasonably accurate measurements hav been obtained the temptation of overem phasis must be avoided Other factor such as the uterine power and the size ar moldability of the fetal head influence t outcome of labor Inability to express th other factors in quantitative terms d not detract from their importance T reluctance with which certain obstetric and radiologists accept roentgen pelvim probably originates in bitter experi resulting from overemphasis of birth c dimensions

Obstetric Roentgenography

THE fetal skeleton and its relationship to the maternal pelvis is easily demonstrated on films of the pregnant uterus Certain measurements of fetal parts may be obtainable By this means an estimate of fetal age and size may be obtained However, it must be recognized that such a report represents only an estimate based on statistical study The estimate of fetal age is cient accuracy to be clinically v Estimates of fetal weight are so in that they are of little or no clinical ance Examination of the pregnar may reveal certain congenital ano the fetus thus providing inform great importance for the conduct

47. DIAGNOSTIC RADIOLOGY

Role of the Radiologist

THE radiologist is most useful in medicine when his efforts are guided by a genuine interest in the cure of each patient Only by this means will roentgenographic examination be of maximum value in permitting diagnosis of the patient s disease and assisting with the plans for treating it The best result will not be obtained when the radiologist merely reports what he sees in the films without knowledge and consideration of the other clinical findings

The radiologist s training makes it possible for him to devise adaptations of apparatus and method for application in special problems Most examinations can be adequately accomplished under the limitations imposed by a standard operating procedure However, the special problem requires the resourcefulness which the radiologist may draw from his knowledge of anatomy, of pathology, and of roentgen ray physics The maximum patient benefit which the roentgen ray department may provide is not realized unless the radiologist is able to apply himself directly to these special cases The development of the science of radiology has followed from such personal application Our standard procedures of today were but short time ago the means devised by some resourceful physician to solve the problem of that moment The standard procedures of tomorrow will evolve from the devices born to solve the special problem of today

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ether for the arm to lung time Determination of the circulation times is frequently performed at the same time as the venous pressure By mixing 5 drops of ether and 5 cc of sodium dehydrocholate solution in the syringe, both arm to lung and arm to tongue times may be done at the same time In the presence of bronchial asthma sodium dehydrocholate is contraindicated and calcium gluconate or aminophyllin may be used

The patient is carefully rehearsed to enable him to respond promptly when he detects ether on his breath and when the bitter taste of the sodium dehydrocholate reaches the tip of the tongue With the patient supine, the mixture of ether and sodium dehydrocholate is injected rapidly into an antecubital vein with an 18 gauge needle The time from the completion of the injection to the detection by the patient of the ether on his breath is the arm to lung time The time to the detection of the bitter taste on the tip of the tongue is the arm to-tongue time The normal value of the arm to-lung time is 4 to 6 seconds, of the arm to-tongue time, 10 to 18 seconds

Interpretation of Results Arm to lung time or the right heart time measures the rapidity of the circulation from the antecubital vein to the pulmonary capillaries The arm to tongue time is a measure of a circulatory cycle from the periphery through right heart, lungs left heart, and back to the periphery The left heart time, or the time necessary for the blood to pass from the pulmonary to the lingual capillaries is determined indirectly by subtracting the arm to lung from the arm to tongue time The normal value is 4 to 10 seconds In left heart failure the arm to-lung time right heart) is normal, whereas the lung o tongue time (left heart) is increased In ailure of both the right and left heart the m to lung and arm to tongue times are th increased in direct proportion to the gree of failure In cor pulmonale the

arm to lung time is increased I minations are frequently prolong strictive pericarditis

Occasionally determination of to-tongue time is useful when a left shunt exists in patent forame This condition may shorten the tongue time No decrease will be o in an interventricular septal defect shunt is usually from left to right arm to-lung time also may be useful right to left shunt as ether in the sys circuit may produce paraesthesias in skin of the head and face, accompanied a stinging or burning sensation for a seconds Chronic pulmonary insufficien not complicated by heart disease will n prolong the circulation time It is therefore of considerable value in the differential diagnosis of cardiac from pulmonary asthma It is prolonged in asthma of cardiac origin but normal or shortened in bronchial asthma and emphysema The circulation time may help to differentiate ascites due to cardiac failure from ascites of other origin

HYPERTENSION

Surgical and dietary modes of therapy for the treatment of hypertension have necessitated more accurate determinations of the responses of blood pressure Patients with hypertension frequently show wide ranges of variation Transient elevation of blood pressure as well as tachycardia due to excitement or nervousness have been shown to be precursors of fixed hypertension

Since it has been shown that the more labile the blood pressure the better is the response to sympathectomy, various procedures have been devised to determine the degree of lability of the blood pressure to aid in selection of patients for operation These include frequent measurements of the blood pressure during the day and night, the cold pressor test the postural

test the sodium amytal test, the use of tetraethylammonium chloride paravertebral block and continuous caudal anesthesia These methods determine the reactivity of the vascular bed and the severity and type of hypertension Obviously it is important to exclude known causes of hypertension such as chronic nephritis pyelonephritis polycystic disease coarctation of the aorta pheochromocytoma pituitary and adrenal cortical tumors and periarteritis nodosa

Sodium Amytal Test

The average control blood pressure is recorded After a light supper the patient is put to bed in a quiet room and given 0 2 Gm of sodium amytal orally at 7 00 8 00 and 9 00 P M Hourly blood pressure and pulse rate determinations are made from 7 00 P M to 7 00 A M The lowest reading of the systolic and diastolic pressure is taken as the response

A fall in blood pressure to normal or near normal levels may presage a favorable response to sympathectomy

Cold Pressor Test

This test was originally devised as a method of determining which patients subsequently might develop hypertension It is also an important indication of the lability of the blood pressure

The patient rests in a supine position for one hour in a quiet room The mean control blood pressure is taken One hand is immersed to above the wrist in ice water (1° C) The blood pressure is then taken in the opposite arm at thirty and sixty seconds The hand is then removed from the ice water and readings are taken every two minutes until the control blood pressure is reached

Interpretation of Results The types of response fall into three groups

1 *The normal hyporeactor* The rise in blood pressure is 20 mm Hg systolic and 15 mm diastolic or less

2 *The normal hyperreactive group in normotensive individuals* There is a mean increase of 30 mm Hg systolic and 25 mm diastolic. The probability is that individuals in this group are potential hypertensives

3 *Patients with essential hypertension* The mean rise is 40 mm Hg systolic and 34 mm diastolic

The degree of the rise in pressure is considered to be of importance in relation to sympathectomy as well as in ultimate prognosis Smithwick considers that the wider the pulse pressure the poorer is the statistical likelihood for lowering the blood pressure following sympathectomy The test is however of greater value as an indication of the subsequent development of hypertension than in the prognosis of the efficacy of sympathectomy

Postural Test

A control reading is obtained The patient remains supine in a quiet room for one hour The blood pressure and pulse is then taken every minute for five minutes The patient then stands and blood pressures and pulse rates are taken immediately and at one-, two, and three minute intervals

Interpretation of Results The normal response is a fall in systolic blood pressure of not more than 20 mm Hg and a rise in diastolic blood pressure of 10 mm The pulse rate should not increase more than 30 beats per minute

In orthostatic hypotension the systolic blood pressure falls below 100 mm Hg There is some fall in the diastolic pressure and the pulse rate shows a marked increase Orthostatic hypotension has been differentiated from postural hypotension in that the fall in systolic and diastolic pressure in the latter is associated with no change in the pulse rate Syncope may occur in ortho

static hypotension but not in postural hypotension

During all blood pressure-lowering procedures it is important to observe the patient for evidence of coronary insufficiency as a result of the fall in blood pressure Symptoms of angina and electrocardiographic changes may occur during the period of fall in tension

Hypertensive Diencephalic Syndrome

A histamine test has recently been suggested to identify patients with the diencephalic type of hypertension described by Page

With the patient in the recumbent position 0 25 cc of histamine acid phosphate solution (0 25 mg of histamine base) is injected intradermally into the skin of the forearm A positive reaction occurs within fifteen minutes and consists of the following each graded + to ++++ based on intensity flushing of the face, headache tearing or lacrimation blotchy erythema of the face and chest, back and abdomen a local reaction consisting of a wheal and erythema at the site of injection The total reaction, based upon an evaluation of the above mentioned findings, is graded as negative or + to ++++ The blush is given greatest weight in this estimation

Interpretation of Results The test is considered of value in estimating the degree and presence of the 'neurogenic' *elements in cases of hypertension It is also* suggested that the test may be of value in the selection of patients for sympathectomy Those reacting strongly to the test showed a favorable response to sympathectomy

Usefulness of Tests

The validity of the various tests has been questioned for different reasons Their prognostic value in regard to longevity and as indications of the success of sympathectomy is not established Continuous caudal anesthesia is preferred by some to the tests given but has been criticized as being too irregular in its effects to be of clinical value in the selection of patients for sympathectomy An increasing realization of the importance of psychogenic factors in the etiology of essential hypertension suggests that a psychiatric evaluation may be more important than any of the tests given

PHEOCHROMOCYTOMA

The presence of a pheochromocytoma should be excluded in cases of suspected essential hypertension It is significant that only 27 per cent of cases of this tumor of the adrenal medulla will show paroxysmal or intermittent hypertension The remainder have chronic hypertension Various tests have been devised to exclude a pheochromocytoma These include the benzodioxane test, histamine test, epinephrine test and perirenal insufflation of air Perirenal insufflation is technically difficult and somewhat hazardous Since at least 15 per cent of these tumors are extraadrenal and inasmuch as the roentgen ray interpretation following insufflation is prone to error the procedure has limited value (p 1079)

BENZODIOXANE TEST

Benzodioxane (933F) is an adrenolytic compound of the Fourneau series It acts to neutralize the increase in circulating epinephrine in the presence of a pheochromocytoma The test is applicable to cases with sustained hypertension

The patient lies in the supine position in a quiet room for a period of twenty to thirty minutes Ten milligrams of benzodioxane per square meter of body surface is introduced intravenously as a 1-2 per cent solution during a two minute period The body surface is obtained from nomograms when height and weight are known Blood pressure readings are taken at intervals of two to three minutes during the preinjection period and at one and at one half minutes before the injection of benzodioxane For the first five minutes

thereafter readings are made at one half minute intervals and then at one minute intervals until the blood pressure returns to preinjection levels This usually occurs in less than fifteen minutes

A fall in blood pressure of 50 mm Hg systolic or more within a few seconds to four minutes is a positive result Toxic reactions which have been observed are flushing palpitation nervousness cold and clammy extremities hyperpnea mild head ache fright and dizziness These usually last less than three minutes

Histamine Test

In patients with paroxysmal or labile hypertension this test is of value in the diagnosis of pheochromocytoma

The patient lies in the recumbent position for thirty minutes Histamine base (0 05 mg in 0 5 cc of isotonic solution of sodium chloride) is injected intravenously Blood pressure determinations are done at one minute intervals for ten to fifteen minutes A cold pressor test is also performed on these patients for comparison

Interpretation of Results A positive reaction suggestive of pheochromocytoma is a blood pressure rise of approximately 100 mm Hg greater than the elevation with the cold pressor test accompanied by characteristic symptoms of a spontaneous attack of paroxysmal hypertension In normal and hypertensive individuals the blood pressure rise is less than the elevation obtained by the cold pressor test Untoward effects are flushing of the face with subsequent headache which is most intense in patients with severe hypertension and pronounced tachycardia False positives have been obtained in individuals with labile hypertension

CORONARY INSUFFICIENCY

The occurrence of angina pectoris as an expression of coronary insufficiency without evidence of physical or electrocardiographic abnormality is well known The history is of paramount value but objective confirmation is always desirable Various methods have been suggested to obtain confirmation of the history These are of limited value and not entirely without danger In certain cases they are indicated

Epinephrine Test

Epinephrine 0 5 cc of a 1 1000 solution is injected subcutaneously A positive test is the production of angina within five minutes It is usually accompanied by a rise in pulse rate and blood pressure An electrocardiogram taken at the time of the anginal episode may reveal ST segment and T wave changes of diagnostic value Nitroglycerine is given to relieve the attack if it occurs

Exercise Test (Feil and Pritchard)

The electrocardiogram is presumably normal It should include standard leads precordial leads and augmented unipolar limb leads The patient walks two steps up and down until pain or dyspnea develops The electrocardiogram is repeated immediately two and four minutes after exercise or until the findings return to normal Symptoms of coronary insufficiency may appear more rapidly if the test is performed after a meal in a cool room or if an ice cube is grasped in the hand

Minor changes may occur in normal controls after exercise These include depression of the RS T segment of less than 1 mm in the limb leads and less than 2 mm in the chest leads diminution or increase in the height of the T wave a change in T 3 to the opposite direction

Abnormal changes in the electrocardiogram after exercise are

1 RS T depression of more than 1 5 mm in the limb leads and 2 mm in lead CR4
2 Typical picture of myocardial infarction
3 Bundle branch block
4 Change in opposite direction of the T wave excluding lead 3

Interpretation of Results The changes are transient and usually disappear within five minutes after completion of the test They may appear with dyspnea and in the absence of angina A negative test does not exclude coronary artery disease The test should not be performed on patients with recent myocardial infarction or myocardial failure

Exercise Test (Master)

The patient walks two steps up and down a standard number of times in ninety seconds—determined from a performance table based on sex, weight, and age (Table 63) Electrocardiograms are taken before and after exercise This is also a test of cardiac function which involves the response of the blood pressure and pulse to a standard number of climbs dependent on the sex weight and age

Abnormal changes are

1 A depression of the RS T segment of more than 0 5 mm in any lead
2 A change from an upright T wave to an isoelectric or inverted T wave
3 A change from a negative T wave to an upright one
4 The occurrence of an arrhythmia
5 Any increase in pulse or blood pressure beyond ten points of resting normals two minutes after exercise

Anoxemia Test

The basis for this test is the observation that anoxemia produces electrocardiographic changes in patients with coronary insufficiency which are more marked than in normal subjects

The patient lies quietly in bed for thirty minutes He is told that if he experiences pain in the chest arms or abdomen during the test to raise his hand immediately A control electrocardiogram employing standard leads and lead CF_4 is taken The patient breathes a mixture of 10 per cent oxygen and 90 per cent nitrogen and tracings are taken at intervals of ten to twenty minutes after the beginning of the test The standard test period is twenty minutes but if pain is felt or there is any other undesirable reaction an electrocardiogram is taken immediately and 100 per cent oxygen is administered for one to two minutes

Interpretation of Results The test is positive if one of the following is present

1 The sum of the RS T deviation in all four leads is greater by 3 mm or more than the control
2 There is partial or complete reversal of the direction of the T wave in lead I accompanied by an RS T deviation of 1 mm or more in this lead
3 There is complete reversal of the direction of the T wave in lead CF_4 regardless of any associated RS T deviation in this lead

This test should not be performed in the presence of congestive failure or if cardiac infarction is known to have occurred at any time in the past It is not without danger and should be performed with care A negative reaction does not exclude coronary disease The result of a test during which pain occurs but electrocardiographic changes are absent is reported as negative

DILATATION OF THE PUPILS

Examination of the fundi is an essential part of every cardiovascular examination Fundal changes may be an indication of the efficacy of therapy in the treatment of hypertension by a salt poor diet a rice diet or sympathectomy If the patient is examined in a dark room dilatation usually is not necessary A thorough examination may require the use of a mydriatic The following procedure is innocuous and rapid

A drop of 1 per cent pontocaine solution is instilled into the conjunctival sac. This is followed in two minutes by a drop of 10 per cent neo synephrine solution

TABLE 63 MASTER'S "TWO-STEP" EXERCISE TEST
Standard Number of Ascents

	Age												
Weight	*5–9*	*10–14*	*15–19*	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*65–69*
						MALES							
40– 49	35	36											
50– 59	33	35	32										
60– 69	31	33	31										
70– 79	28	32	30										
80– 89	26	30	29	29	29	28	27	27	26	25	25	24	23
90– 99	24	29	28	28	28	27	27	26	25	25	24	23	22
100–109	22	27	27	28	28	27	26	25	25	24	23	22	22
110–119	20	26	26	27	27	26	25	25	24	23	23	22	21
120–129	18	24	25	26	27	26	25	24	23	23	22	21	20
130–139	16	23	24	25	26	25	24	23	23	22	21	20	20
140–149		21	23	24	25	24	24	23	22	21	20	20	19
150–159		20	22	24	25	24	23	22	21	20	20	19	18
160–169		18	21	23	24	23	22	22	21	20	19	18	18
170–179			20	22	23	23	22	21	20	19	18	18	17
180–189			19	21	23	22	21	20	19	19	18	17	16
190–199			18	20	22	21	21	20	19	18	17	16	15
200–209				19	21	21	20	19	18	17	16	16	15
210–219				18	21	20	19	18	17	17	16	15	14
220–229				17	20	20	19	18	17	16	15	14	13
						FEMALES							
40– 49	35	35	33										
50– 59	33	33	32										
60– 69	31	32	30										
70– 79	28	30	29										
80 –89	26	28	28	28	28	27	26	24	23	22	21	21	20
90– 99	24	27	26	27	26	25	24	23	22	22	21	20	19
100–109	22	25	25	26	26	25	24	23	22	21	20	19	18
110 119	20	23	23	25	25	24	23	22	21	20	19	18	18
120–129	18	22	22	24	24	23	22	21	20	19	19	18	17
130–139	16	20	20	23	23	22	21	20	19	19	18	17	16
140–149		18	19	22	22	21	20	19	19	18	17	16	16
150–159		17	17	21	20	20	19	19	18	17	16	16	15
160–169		15	16	20	19	19	18	18	17	16	16	15	14
170–179		13	14	19	18	18	17	17	16	16	15	14	13
180–189			13	18	17	17	17	16	16	15	14	14	13
190–199			12	17	16	16	16	15	15	14	13	13	12
200–209				16	15	15	15	14	14	13	13	12	11
210–219				15	14	14	14	13	13	13	12	11	11
220–229				14	13	13	13	13	12	12	11	11	10

From the *American Heart Journal* 10.497 1935

Dilatation is usually complete in twenty to thirty minutes Pilocarpine is not necessary for the production of myosis following the procedure as the action of "neo synephrine is brief and does not elevate intraocular tension

ARTERIAL PUNCTURE

This procedure is useful for the determination of the arterial oxygen saturation It is of value for culture of arterial blood where septicemia in subacute bacterial endocarditis is suspected despite repeated negative venous blood cultures It is helpful where phlebotomy is difficult because of increased blood viscosity (as in polycythemia) or where venipuncture is not possible because of poor or thrombosed veins It may also be used for intra arterial injections

The brachial or femoral artery is usually employed Local infiltration with 1 per cent procaine may be done A sharp needle, 18 or 20 gauge preferably a special arterial puncture needle of the Cournand type, is employed When the brachial artery is used the artery is palpated with the forearm fully extended midway between pronation and supination and the vessel is entered as in venipuncture Following withdrawal of the needle pressure is maintained over the site of the puncture for five minutes A pressure bandage is then applied Active motion of the extremity should be avoided for a twelve hour period to prevent hemorrhage Repeated punctures may be made

PERICARDIAL PARACENTESIS

In pericardial effusions of unknown etiology, diagnostic paracentesis is valuable It may also be indicated therapeutically in cases of cardiac tamponade

An 18 gauge blunt spinal tap needle is used The site selected is the fifth left intercostal space at the outer border of cardiac dullness This should be checked by fluoroscopy This position is usually between the apex and left border of the heart Following preparation of the skin and infiltration with procaine, the needle is inserted cautiously in the direction of the spine The usual depth is 3–4 cm but depends on the thickness of the chest wall If the heart is beating against the needle, the needle is withdrawn slightly and fluid withdrawn If the tap is unsuccessful at this site the fourth or fifth interspace just to the left of the sternum or the fourth interspace to the right of the sternum may be employed The subxiphoid approach and the left posterior thoracic wall may also be employed as sites of puncture Occasionally failure at one site will be attended by success at another Usually 200–500 cc are removed at the first tap

The fluid is examined for specific gravity, protein content and cell count A smear and a culture are made

VENISECTION (CUT-DOWN TECHNIC)

When venipuncture cannot be performed because of poor or thrombosed veins it is sometimes necessary to cut down on a vein This is usually done in the antecubital space The skin is prepared with antiseptics and 1 per cent procaine solution is injected A 2 cm transverse incision is made One of the large veins is dissected free from the surrounding tissue The needle is inserted and the indicated procedure performed Catgut sutures are tied above and below the site of puncture The skin is then approximated with interrupted sutures

This procedure may also be indicated therapeutically for phlebotomy in patients with pulmonary edema and polycythemia

HYPERACTIVE CAROTID SINUS TEST

Hypersensitivity of the carotid sinus occurs in certain individuals and produces fainting fall in blood pressure or slowing of the heart rate The attack may occur

spontaneously It may be precipitated by wearing a tight collar or turning the head Reproduction of symptoms by pressure on the carotid sinus confirms the diagnosis and serves to avoid confusion with other conditions such as coronary disease

The carotid sinus is at the bifurcation of the common carotid artery which is at the level of the hyoid bone The patient is placed in a recumbent or sitting position if the latter is used precautions are taken to prevent injury from syncope Pressure is exerted first on the right artery compressing the vessel against the cervical spine for five to ten seconds This is repeated on the left side if indicated both vessels may be compressed simultaneously Auscultation of the heart is done during the maneuver and the blood pressure is taken during or immediately following it If asystole occurs the pressure should be released immediately

The same procedure is followed to terminate an attack of paroxysmal auricular tachycardia

ANTISTREPTOLYSIN TEST

This test is of value chiefly to distinguish an attack of rheumatic fever from rheumatoid arthritis Streptolysin O is formed by most members of Group A streptococci by human Group C strains, and by the large colony forms of Group G The fact that streptolysin loses its hemolytic property when neutralized with immune sera forms the basis for the quantitative test for antistreptolysin Twenty cc of whole blood are required.

Interpretation of Results An antibody titer of 250 units or over in a young adult is positive and indicates a recent hemolytic streptococcus infection (A unit is the reciprocal of the fraction of 1 0 cc of serum required to neutralize two and one half minimum hemolytic doses [M H D] of hemolysin) An increase in antistreptolysin occurs after streptococcus sore throat due to Group A streptococci, acute rheumatic fever, scarlet fever, and acute glomerular nephritis The fact that normal titers are the rule in rheumatoid arthritis serves as a valuable differential point A significant response usually occurs on the eighth to tenth day of the disease and at the end of the fourth week, when the antibody response is maximal A rising titer is of special significance Below three years and above forty years of age, the normal values are uniformly low (150 units or below) Of patients infected with hemolytic streptococci 85 to 90 per cent develop demonstrable amounts of antistreptolysin O which may persist for months or years

C-REACTIVE PROTEIN

The determination of C reactive protein is a sensitive indication of the activity of the disease process in acute rheumatic fever It is based on the finding that the somatic C polysaccharide of the pneumococcus reacts with a protein to form a precipitate when added to acute phase sera of patients with acute rheumatic fever A specific rabbit antiserum has been made against C reactive protein the use of which has increased the sensitivity of the test

The precipitin reaction involved is graded 0 to ++++++ Other acute infections such as scarlet fever rheumatoid arthritis subacute bacterial endocarditis staphylococcus, pneumococcus and gram negative bacillary infections of the colon typhoid group may give a positive test It is therefore of no value in differential diagnosis The C-reactive protein determination is however probably the most sensitive measurement of activity of rheumatic infection

ELECTROCARDIOGRAPHY

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The precipitin reaction involved is graded 0 to ++++++. Other acute infections such as scarlet fever, rheumatoid arthritis, subacute bacterial endocarditis, staphylococcus, pneumococcus and gram-negative bacillary infections of the colon-typhoid group, may give a positive test. It is therefore of no value in differential diagnosis. The C-reactive protein determination is, however, probably the most sensitive measurement of activity of rheumatic infection.

ELECTROCARDIOGRAPHY

Special Leads

In addition to the standard leads, precordial leads should be taken routinely. If cardiac disease is not suspected, three precordial leads—usually V2, 4 and 6 or V1,

3, and 5—are taken In suspected cardiac disease, six precordial leads are desirable The CF leads are also employed, but V leads are probably more useful They vary slightly from the CF leads and, therefore, when repeated tracings are taken, the same type of precordial leads, CF or V, should be used These leads are chiefly of value in anterior or lateral wall myocardial infarctions and in bundle branch block When large P waves are desired in patients with an arrhythmia, the CR lead should be employed in the third interspace just to the right of the sternum with double sensitivity of the string With the electronic tube electrocardiograph, the sensitivity control is turned up to obtain a maximum deflection for one millivolt of current This generally measures about 15 mm or one *and one-half times the standard*

Stimulation of the vagus by carotid sinus compression, while this lead is taken may aid in diagnosis by abolishing paroxysmal tachycardias or by producing an increase in auriculoventricular block in auricular flutter and tachycardia By slowing the rate in this fashion, P waves previously buried in preceding T waves or in corresponding QRS or T complexes may be revealed

Esophageal Leads

These are not employed routinely They are of value chiefly when involvement of the posterior aspect of the left ventricle is suspected and the standard leads are not diagnostic In this situation the precordial leads are generally of little value as the exploring electrode is quite removed from the involved area Esophageal leads are also useful for securing distinct P waves in arrhythmias

A special electrode is inserted through the nose into the esophagus It is coupled through a central terminal with one of the extremities Tracings are taken ordinarily at intervals of 5 cm to the 60 cm mark from the nares The position of the auricle is identified by P waves of large amplitude with an intrinsic deflection and is usually at the 35–40 cm mark The changes in the region of the ventricle in damage to the posterior aspect of the left myocardium are similar to those seen with anterior wall infarctions as taken with the precordial leads

Unipolar Limb Leads

These leads determine the electrical potential at each of the three extremities Three leads are taken The exploring electrode is placed above the right wrist (Vr) left wrist (Vl), and above the left ankle (Vf) The indifferent electrode is formed by connecting the right arm left arm and left leg electrodes to a central terminal through a resistance of 5000 ohms Augmented unipolar extremity leads of Goldberger increase the amplitude of the deflections by 50 per cent and are alleged to reflect more accurately the potentials in the limb leads These are known as aVr, aVl and aVf

Interpretation of Results The unipolar limb leads are of value to determine the electrical axis or rotation of the heart They furnish supplemental information in cases of myocardial infarction and bundle branch block Lead aVf has been considered helpful in determining whether or not Q3 is abnormal Goldberger's criteria are as follows

1 The Q wave in aVf normally should not exceed 60 per cent of the corresponding R wave
2 It should be less than 0 04 of a second
3 In association with (1) and (2) aVr shows an RS pattern but not a QR pattern except if there has been a previous anterior wall infarct

These leads aid in differentiating posterior wall infarcts from pulmonary embolism They serve to elucidate the mechanism of formation of the standard limb leads and the differences in *various* precordial leads

ANGIOCARDIOGRAPHY

Fluoroscopic examination of the heart with a barium swallow in the posteroanterior view and the right and left oblique positions affords valuable information concerning chamber enlargement and the large vessels However, fluoroscopy has obvious limitations and occasionally further information is necessary This may be obtained by means of the injection of radiopaque material into the heart and great vessels through an antecubital vein, and visualization of these structures by radiographs

A special Robb Steinberg 12 gauge needle with attached three way stopcock is employed 'Diodrast (25 to 40 cc of a 70 per cent solution) is injected rapidly (in two seconds) into an antecubital vein Frequently, it is necessary to cut down on the vein To avoid necrosis it is essential that none of the solution escapes into the surrounding tissues The arm to-lung and arm to-tongue time to determine the circulation rate to the right and left heart is of aid in timing the exposures The average time for passage of the contrast medium to the various structures is as follows

Vena cava and right atrium 1½ seconds
Right ventricle and pulmonary tree 3 seconds
Pulmonary veins and left atrium 6 8 seconds
Left ventricle and thoracic aorta 8–10 seconds

A 35 or 70 mm photoroentgen unit is de[sirable] for rapid serial views although a [st]ereoscopic cassette changer can be used The superior vena cava and its tribu[tar]ies, the four chambers of the heart and [their] walls the ventricular septum, pul[mo]nary and aortic valves the pulmonary [circ]ulation, thoracic aorta and branches [can] be visualized The abdominal aorta is [usua]lly not satisfactorily seen because of [diluti]on of the contrast medium Direct [injecti]on of the abdominal aorta through [a post]erior approach has been done and is [useful] in special situations

[Complica]tions are seldom serious Dizziness [...]ss, nausea vomiting sweating hypotension, and syncope are not unusual The procedure is contraindicated in the presence of severe disease of the liver or kidney and in hyperthyroidism It is not advisable in circulatory failure or in critically ill patients

Angiocardiography has provided helpful information in tumors of the mediastinum, aneurysm of the aorta, congenital heart disease, cor pulmonale, atrial enlargement, and pericardial effusion

PHONOCARDIOGRAPHY

The phonocardiograph or stethocardiograph is an apparatus for the amplification and photographic registration of heart sounds and murmurs An electrocardiogram is taken synchronously Simultaneous registration of heart sounds and the electrocardiogram is of value in timing heart sounds and murmurs in their relation to the cardiac cycle The character and intensity of heart sounds may also aid in the diagnosis of heart block, nodal premature beats and paroxysmal ventricular tachycardia Pulsus alternans may also be recorded Although it has limited clinical application, it is useful in teaching

CARDIAC CATHETERIZATION

The complex procedures involved in the use of cardiac catheterization as a diagnostic technic are not applicable to general use Important information of value in the diagnosis and treatment of congenital and pulmonary heart disease is obtained The success of therapy following cardiac surgery may be gauged by the procedures associated with cardiac catheterization The determination of pressures in the right heart, and the oxygen content of blood in the superior vena cava right atrium, right ventricle, and the pulmonary arteries indicate the presence, location, and type of obstruction or shunt The development of the oximeter has made possible the continuous determi

nation of the arterial oxygen saturation during standard exercise and following the inhalation of 100 per cent oxygen. The comparison of the oxygen content and saturation of peripheral arterial and pulmonary capillary blood, following the standard exercise test and the inhalation of oxygen, will indicate the direction of blood flow in shunts, and the degree of blood flow through the shunt These technics are of aid in the precise diagnosis of patent ductus arteriosus, pulmonic stenosis, interatrio-septal defects, interventricular septal defect, and pulmonary hypertension Description of the technics involved are beyond the scope of this chapter

Peripheral Vascular Disease

OBSERVATION and palpation of the extremities for blanching cyanosis, rubor, trophic changes, and arterial pulsation are of inestimable value in the diagnosis of peripheral vascular disease The factor of vasospasm is of great significance in the determination of the presence and extent of impairment of the peripheral circulation Various chemical and physical means are employed in the elimination of vasospasm to determine organic occlusive disease Among the chemical methods, the use of 'priscoline, tetraethylammonium chloride, and the intra arterial injection of papaverine are of value Among the physical methods, the following are helpful elevation of body temperature peripheral nerve block, parasympathetic block caudal anesthesia, spinal anesthesia, and general anesthesia These procedures produce temporary abolition of vasconstrictor tone in the extremities

LANDIS GIBBON'S TEST

This employs the principle of elevation of body temperature for elimination of vasospasm Under basal conditions, the patient lies thinly clad in a room at a temperature between 18° and 21° C When the digits have cooled the body temperature is raised by surrounding the body with electric pads and blankets or by placing the patient in an electrically heated cabinet except for the limbs under observation An alternative procedure is to immerse two uninvolved limbs in water at a temperature of 42° to 44° C for thirty five minutes

With abolition of vasoconstrictor impulses, there is dilatation of normal vessels and increase in peripheral blood flow The digital skin temperature is taken with an electrical thermometer such as the 'dermolor, or a thermocouple The normal response is a rise in skin temperature to between 30° and 33° C It indicates the absence of significant organic arterial disease A partial response is a rise in skin temperature to 27° to 29° C indicating moderate organic vascular disease Advanced occlusive arterial disease is indicated by an absence of vasodilatation and its attendant increase in skin temperature

PERIPHERAL NERVE BLOCK

When warming fails to produce the vasodilatation, peripheral nerve block may be employed It is simple and effective

In the upper extremity, the ulnar nerve is injected at the elbow with 1 per cent procaine solution The median nerve is injected at the wrist For the lower extremity the posterior tibial nerve is interrupted as it passes behind the internal malleolus at the ankle The common peroneal nerve is injected just below the head of the fibula The rise in skin temperature is directly

proportional to the degree of vasodilatation

PARAVERTEBRAL BLOCK

The use of procaine hydrochloride to interrupt sympathetic ganglia is an effective method for securing peripheral vasodilatation and abolishing vasoconstrictor tone Hence it is of value both for diagnostic and therapeutic purposes This procedure is described elsewhere in this book *

NORMAL SURFACE TEMPERATURES

The average value is 32 5° C for the torso with a reduction of 1 to 2° for the upper extremities and 2 to 3° for the lower extremities The range of temperature variations over the body is 4 to 5° over the hands, 4 to 6° and over the feet 6 to 8°

Information as to the extent and site of organic arterial occlusion is afforded by the use of the histamine flare test the reactive hyperemia test of Pickering the Allen test the oscillometer and arteriography

HISTAMINE FLARE TEST

The rationale for this test is the observation that the speed at which wheals form following the intradermal injection of histamine is dependent on the rate of blood flow

With the extremity in the horizontal position, 0 1 cc of 1 2000 dilution of histamine is injected intracutaneously in 0 5 per cent procaine solution In the lower extremity the histamine is injected into the dorsum of the foot just above the inner side of the ankle at the middle of the calf and below and above the knee A wheal normally develops at the end of five minutes when the first reading is made A delay beyond this time is evidence of impairment of the circulation

This test is believed to be of value in following the effects of therapy and as an indication of the level for amputation in occlusive arterial disease In the presence of vasospasm, the test is unreliable, so spasm must first be eliminated The test is dependent on cutaneous blood flow only, and gives no indication of the state of circulation in the muscles

REACTIVE HYPEREMIA TEST

Dilatation of arterioles is achieved by immersing the extremities in water at 35 to 40° C for ten minutes The extremity is elevated and the circulation is arrested by a blood pressure cuff inflated above the systolic blood pressure for five minutes Normally, release of the circulation is followed by a hyperemic flush which reaches the tips of the digits in less than five seconds In the presence of organic occlusion, the flush is delayed and faint The test has been criticized because compression of diseased arteries may result in thrombosis

ALLEN TEST

This determines the patency of the ulnar artery

The hand is held above the head until blanching occurs The radial artery is compressed and with the pressure maintained the patient s hand is brought down The resulting color is observed Persistence of blanching indicates closure of the ulnar artery Prompt return of color indicates patency of the vessel

OSCILLOMETER

This instrument consists of a pneumatic cuff which is placed around the extremity and is connected to an instrument for measuring—in arbitrary units—changes in the amplitude of pulsation in the limb

The cuff is placed at the desired level around the extremity, and is inflated until no movement of the needle indicator is observed The pressure is then dropped in steps of approximately ten units The in

* See Chapter 44

portant point is that of maximum pulsation *The amount of pulsation at that point* should be recorded The normal values according to Samuels, are as follows

Axillary region 4–20
Brachial region 2–1[illegible]
Wrist 1–10
Palm 0 5–2
Upper Thigh 4 16
Lower thigh 4 14
Calf 3–10
Ankle 1–10
Foot 0 5–4

Interpretation of Results The oscillometer has been used to estimate the exact level of arterial occlusion and to determine the presence or absence of pulses which are difficult to palpate because of the surrounding tissues The value of oscillometric readings is limited because considerable variation in the same limb may be found in normal individuals The magnitude of pulsations in the small collateral vessels generally present in a diseased extremity with rigid arteries is not recorded Therefore local blood flow may not be markedly impaired in the face of low readings Determination of skin temperatures may be helpful in this situation It is also true that data obtained from legs or arms cannot be applied with accuracy to the state of the circulation of the toes or fingers Spasm cannot be differentiated from organic occlusion Hence the method is chiefly of value in following the course of the patient and in determining the effects of vasodilatation procedures

ARTERIOGRAPHY

This procedure may be helpful in the diagnosis of organic obstruction and in the determination of the level of the obstruction

A blood pressure cuff is inflated above the systolic pressure In the upper extremity the brachial artery is punctured as indicated under technic of arterial puncture Twenty cubic centimeters of 35 per cent 'diodrast are injected A roentgenogram is made immediately The blood pressure cuff is deflated several times to permit the dye to advance, a roentgenogram being made each time In the lower extremity the femoral artery is occluded by digital pressure, and the dye is injected distally The roentgenograms are taken as before the femoral artery pressure being released before each roentgenogram

Interpretation of Results Useful information may be obtained in arteriovenous fistulas and in the differential diagnosis of thromboangiitis obliterans and arteriosclerosis as a characteristic picture is seen in each of these conditions It has been used for the determination of the site of amputation in the presence of gangrene The presence of vasospasm must be considered in the interpretation If the vascular shadow ends in a point occlusion is probably on the basis of spasm If the shadow is blunt and transverse it is indicative of organic obstruction

SCALENUS ANTICUS SYNDROME*

Various tests have been devised for determination of impairment of the circulation of the upper extremity due to pressure of the scalenus anticus muscle with or without the association of a cervical rib The *Adson maneuver is helpful*

Adson Maneuver

The neck is extended with the head turned to the affected side while a deep *breath is taken* This places the scalenus anticus muscle in tension and produces diminution or obliteration of the radial pulse

Modifications include horizontal extension of the arms at the shoulder with flexion of the forearms at the elbows so that the forearm is perpendicular with the head rotated toward or away from the affected side Another suggestion is to have

* See also Chapter 11

the patient assume the position of attention with the shoulders drawn back

TESTS OF VENOUS INSUFFICIENCY

Trendelenburg Test

This procedure yields information concerning the competency of the saphenous valves and of the communicating valves at different levels

With the patient recumbent the extremity is elevated and a tourniquet is applied high over the saphenous trunk With the veins emptied and collapsed and the tourniquet in place the patient stands

Interpretation of Results If the veins remain collapsed it is evidence that the reflux of blood ordinarily occurs from above the level of application of the tourniquet that is the saphenofemoral junction and not from the deep veins through the communicating branches If the veins suddenly fill when the erect position is assumed despite the presence of the tourniquet the communicating valves are incompetent

A positive reaction to this test indicates an advanced stage of venous insufficiency

Perthe's Test

This test determines the patency of the deep veins of the extremity in the presence of varicosities

The patient stands until the veins fill A tourniquet is then applied to the thigh to occlude the saphenous trunk and the patient is told to walk about briskly

Interpretation of Results Normally the blood is aspirated into the deep veins and superficial varicosities promptly collapse This indicates that the communicating veins are competent but the saphenous valves are not If the deep veins are not patent or if there is an increased venous pressure in the deep veins on standing no diminution in size of the distended superficial veins occurs Application of the tourniquet to different levels of the thigh will help determine the site of incompetent valves

Percussion Test

This test indicates the presence of valvular incompetence in the saphenous vein

The varices in the leg are palpated with one hand and with the other, percussion is performed over the saphenous vein in the groin A transmitted impulse is felt by the fingers over the varices in the leg indicating incompetency of the saphenous valves The course and location of the internal saphenous vein near the groin is determined by placing one hand in the region of the groin while the other hand percusses over the varices in the leg

Venography

Visualization of the veins of the extremity by means of contrast media has been advocated in order to determine the presence and site of venous obstruction

In the lower leg 20 cc of 35 per cent diodrast is injected at a rate of 1 cc per *second into the long saphenous vein or one* of its tributaries when visualization of the upper long saphenous the upper femoral, or the iliac veins is desired When visualization of the short saphenous vein the popliteal vein or the lower femoral vein is necessary injection is performed in a superficial vein of the outer aspect of the foot A tourniquet is employed to distend the veins and injection is made through a 21 gauge needle The tourniquet is removed before the injection is made For visualization of the axillary and subclavian veins 10 cc of 35 per cent diodrast are injected into the median basilic vein at a rate of 1 cc per second Roentgenograms are taken during the injection

Interpretation is difficult because of the occurrence of venospasm Venous thromboses as a result of the procedure are rare especially if the vein is washed out with

saline following the injection Nausea and vomiting may occur

Infrared Photography

Following obstruction of a vein of a main venous trunk, there is dilatation of the superficial collateral veins of the region involved With *slowing of the blood stream* the oxygen content is lowered, and the veins photograph more vividly by the infrared method than the normal cutaneous veins Occasionally, this is helpful in determining the extent of *venous collateral circulation*

Tests of Renal Function

RENAL function may be determined adequately for clinical purposes by relatively simple tests carefully performed Different tests reflect damage to the glomerular or tubular portions of the nephron or both Thus the presence of albumin and red blood cells in the urine and diminution in urea clearance are usually indications of glomerular injury Casts in the urine, with the exception of blood casts, reduced values in the concentration test, and the phenol sulfonphthalein test reflect tubular involvement However in most cases of renal disease both elements of the nephron are involved Although the urea clearance and the phenolsulfonphthalein tests apply to functions of different portions of the nephron they usually parallel each other closely The following procedures are useful

URINALYSIS

A morning specimen should be examined shortly after voiding as formed elements dissolve quickly in dilute or alkaline urine and are obscured on standing by the precipitation of crystals Examination of the specific gravity, the reaction, and the presence of albumin and glucose are routine Microscopic examination of the urinary sediment soon after centrifugation is always desirable In hospital practice it is not morally reprehensible for routine purposes to limit the study of the sediment to urines containing albumin A careful study of the sediment when indicated is preferable to a hasty one done as a routine in all cases However, it must be remembered that, rarely, red blood cells and other formed elements may be present in the absence of albumin in the urine

CONCENTRATION TEST

This is an important and sensitive test of tubular function Since inability of the kidney to concentrate urine is among the earliest indications of renal damage, if the specific gravity is normal other tests of renal function are usually unnecessary If a casual specimen has a specific gravity of 1 025 or above, the concentration test need not be performed The test is of no value in a patient who experiences diuresis despite the fluid restriction Inasmuch as *this is primarily a test of tubular function* in certain cases of acute glomerulonephritis and in prerenal azotemia, the specific gravity may be normal despite the presence of nitrogen retention

Food and fluids are withheld from 6 00 P M to noon of the following day The patient voids and discards the specimen before retiring Specimens of urine are collected at 8 00 A M , 10 00 A M , and 12 noon

Normally, the specific gravity is 1 025 or higher Specific gravity between 1 020 and 1 023 indicates slight impairment of concentration power In the presence of *much*

buminuria, the specific gravity should be rrected by subtracting 0.003 multiplied y the percentage of protein

PHENOLSULFONPHTHALEIN TEST

This excretory test measures tubular function and renal blood flow Since the dye is readily excreted by the tubules, the commonly performed two-hour test is not sufficiently sensitive to anything but extreme impairment of renal function On the other hand, the intravenous fifteen minute test is sensitive

To obviate difficulty in obtaining urine specimens, the patient should not void at the beginning of the test The patient drinks 600 cc of water After thirty minutes, exactly 1 cc (6 mg) of the dye is injected intravenously The urine specimen is collected exactly fifteen minutes after the injection The normal value is 25 per cent or more

Interpretation of Results In advanced lesions the excretion is 10 per cent or less The amount of urine should be more than 50 cc since adequate diuresis is necessary for accuracy Decreased excretion reflects a decrease in renal mass and an associated reduction in blood flow There is good correlation between this test and the urea clearance

UREA CLEARANCE TEST

This is a test of glomerular filtration When the specific gravity is fixed further determination of the extent of renal damage may be done by means of the urea clearance test This procedure is based on the quantity of blood cleared of urea per minute At a urine volume of 2 cc or more per minute, the urea excretion is at a maximum value This maximum clearance (*Cm*) averages 75 cc of blood cleared of urea per minute When the output is less than 2 cc per minute, the volume of blood cleared of urea each minute averages 54 cc This is ... clearance (*Cs*) Since the standard clearance varies to a greater degree than the maximum clearance, whenever possible urine volumes of 2 cc or more per minute should be obtained The values are calculated from the following formulas and involve measurement of urea in the blood and urine and measurement of the urine volume

$$(1)\ Cm = UV / B$$
$$(2)\ Cs = U / B \times \sqrt{V}$$

where U = Urea in mg per 100 cc of urine
B = Urea in mg per 100 cc of blood
V = The volume of urine excreted in one minute

The values are expressed in percentage of the normal by multiplying by 100 and dividing by the normal clearance, 75 for *Cm* and 54 for *Cs*

The patient is in the recumbent position for the test except for voiding Breakfast need not be withheld Five hundred cubic centimeters of water are given at 8 00 A M and 500 cc at 9 00 A M The patient voids after drinking the first 500 cc of water, the specimen is discarded and the time is noted One hour later, the patient voids completely the specimen is saved and the time recorded At the end of the second hour the patient again voids the time is noted and the urine is saved A blood speci men is obtained at the end of the first hour The patient must void completely and th[e] times be noted accurately, so that th[e] volume per minute can be determined is not essential for the patient to void fixed intervals As long as the exact time voiding is noted, the rate per minute c[an] be calculated

Interpretation of Results The nor[mal] reading varies between 75 to 125 per of the mean Values below 50 per definitely are abnormal

The concentration test will usuall[y] tect impairment of renal function the urea clearance becomes abn[ormal] When the urea clearance is impair[ed] specific gravity of the urine usually

The clearance then may be used to follow the course of the patient The urea clearance will return to normal sooner than the concentration test, following acute nephritis In advanced renal damage, the urea clearance tends to become fixed Clearance values are reduced markedly before nitrogen retention occurs

ADDIS COUNT

This procedure is a quantitative study of the urinary sediment It is valuable in following the course of glomerulonephritis and in determining complete healing following acute nephritis

No fluid is taken from 8 00 A M to 8 00 A M of the following day The patient voids at 8 00 P M and the specimen is discarded The urine is collected from 8 00 P M to 8 00 A M in a bottle containing 5 cc of 4 per cent formalin solution Women must be catheterized

The volume is measured Ten cubic centimeters of urine are centrifuged at 18,000 revolutions per minute for five minutes From 9 to 9 9 cc of the supernatant are pipetted off The remaining sediment is mixed A drop of the suspension is placed in a hemocytometer and the number of casts in all nine squares are counted under low power The number of red blood cells and white blood cells are counted under high power This is repeated two to ten times, depending on the number of casts found If there are few casts, ten drops are counted If the casts are numerous the *sediment is diluted to a fifth* and two drops are counted The total number in the twelve hour specimen is calculated by the formula

$$\text{Number} = \frac{S}{v} \times M \times \frac{V}{10}$$

where S = the volume of mixed sediment in cc
v = the total volume in which counts were made (0 0009 cc × number of fillings)
M = total number of casts or cells counted
V = volume of the twelve hour specimen in cc

Upper limits of normal are 5000 casts, 1,000,000 red blood cells, and 2 000,000 *white blood cells* and epithelial cells in the twelve hour specimen of urine

While the Addis count is too time-consuming for routine use, it is an important technic in special situations. No case of acute nephritis may be considered completely healed unless the Addis count is normal

BLOOD NITROGEN TEST

Determination of the urea nitrogen is *preferred to that of the nonprotein nitrogen*, because of its simplicity The normal value is 10–15 mg per 100 cc The nonprotein nitrogen, creatinine and uric acid tests are not ordinarily performed

Interpretation of Results The blood urea nitrogen becomes elevated relatively late in the course of renal damage For example, it may still be normal when the urea clearance has fallen to 20 per cent of normal In addition the urea nitrogen may be influenced by diet and the degree of hydration Nonetheless, in cases of uremia and prerenal azotemia, successive determinations of the urea nitrogen provide significant information concerning the course of the patient and the influence of therapy

ORTHOSTATIC ALBUMINURIA

In this condition, albumin is excreted while the patient is in the erect position It is obviously important to distinguish this benign state from albuminuria due to renal damage

After voiding and discarding the urine, the patient stays in bed from the time of retiring to 8 00 A M The first specimen is collected at 8 00 A M and the patient becomes ambulant The second and third specimens are collected at 10 00 A M and 12 noon

The presence of albumin in the second

and third specimens, but not in the first, is a positive test The test must be interpreted cautiously in conjunction with other tests as orthostatic albuminuria may presage renal disease It is not always a functional disturbance

URINARY CHLORIDES

A relatively simple but important guide to therapy in cases of dehydration and salt depletion is the determination of the twenty four-hour excretion of sodium chloride in the urine This test may indicate the cooperation of the patient who has been placed on a salt poor diet It is of value in preparing patients for surgery and in postoperative care The patient who requires the administration of sodium chloride will have a low output of chloride in the urine

The daily output of sodium chloride averages 6–10 Gm

In determining the state of electrolyte balance, it is frequently also necessary to obtain the plasma chloride level the bicarbonate total base protein and the hematocrit

NEEDLE BIOPSY OF THE KIDNEY

Needle biopsy and aspiration of renal masses or tumors have been employed successfully These procedures are useful in differentiating tumors from cysts and abscesses Recently, Iversen and Brun have reported on aspiration biopsy of the normal sized right kidney in the investigation of intrinsic renal disorders This procedure is still in the experimental phase

RADIOLOGIC PROCEDURES

The intravenous pyelogram and the retrograde pyelogram are useful procedures to determine gross anatomic abnormalities such as hydronephrosis polycystic disease, renal tumor, and renal lithiasis If the urea clearance is less than 30 per cent there is usually failure of visualization with the intravenous pyelogram This is true when the specific gravity is fixed at 1 010 The test, therefore, should not be performed in these instances or in the presence of uremia When hematuria occurs, with little change in renal function, a pyelogram should always be performed Retrograde injection is contraindicated in acute nephritis

Hematologic Procedures

THE measurement of the size and hemoglobin content of the red blood cells and the values derived from them have wide application in the diagnosis of the anemias Normal variations in hemoglobin in individuals of different sex and age, and in those of the same sex and age make an arbitrary normal value misleading Hence the expression of the hemoglobin in percentage of normal is undesirable, and the quantity of hemoglobin is best stated in grams The absolute values derived from measurement of the size and hemoglobin content of the red blood cells and the hematocrit (volume of packed red blood cells) have been expressed by Wintrobe as mean corpuscular volume mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration These have greater significance than those values derived from arbitrary standards as the volume color, and saturation indices

MEAN CORPUSCULAR VOLUME (M C V)

This is an expression of the volume of the average red blood cell It corresponds to the volume index

$$M\,C\,V = \frac{\textit{Vol packed RBC (cc per 1000 cc)}}{\textit{RBC (millions per cu mm)}}$$

The average normal value in the adult is 87 It varies from 82 to 93 It is expressed in cubic microns (c μ)

Macrocytic anemias produce an increase of the mean corpuscular volume to 95 or more Simple microcytic anemias yield values from 79 to 72 Hypochromic micro cytic anemias usually have an M C V below 72

MEAN CORPUSCULAR HEMOGLOBIN

This index measures the weight of hemoglobin in the average red blood cell or the hemoglobin content of the red blood cell It corresponds to the color index

$$M\,C\,H = \frac{\textit{Hemoglobin (Gm per 1000 cc)}}{\textit{RBC (millions per c mm)}}$$

The average normal value is 29 It varies from 27 to 31 in the adult It is expressed in micromicrograms ($\mu\mu g$) or Gm $\times 10^{12}$

In macrocytic anemias this value varies from 33 to 56 in normocytic anemias 27 to 32 in simple microcytic anemias from 22 to 26 and in hypochromic microcytic anemias from 14 to 21

MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION

This is a ratio of the weight of hemo globin to the volume of packed red blood cells in which it is contained It corresponds to the saturation index

$$M\,C\,H\,C = \frac{\textit{Hemoglobin (Gm per 100 cc} \times 100)}{\textit{Packed RBC (cc per 100 cc)}}$$

The average normal value is 34 per cent It varies from 32 to 36 per cent

Interpretation of Results In most anemias an increase or decrease in the average size of the red blood cell (M C V) is associated with corresponding increases or decreases in the weight of the hemo globin (M C H) The ratio of these to one another is indicated by the mean corpuscu lar hemoglobin concentration, which re mains normal in most anemias except the severe hypochromic anemias, where the index may be reduced to between 21 and 29 In the hypochromic microcytic anemias (iron deficiency), the reduction in weight of hemoglobin in the average red blood cell is even greater than the decrease in average cell size This is indicated by re duction in the M C H C Only reductions below normal in the M C H C have been observed

A nomogram (Fig 13) simplifies the de termination of the corpuscular constants

HETEROPHILE ANTIBODY TEST

An increased titer of agglutinins for sheep red blood cells is found in 50–80 per cent of cases of infectious mononucleosis Others have indicated that increased ag glutinins appear in as high as 92 per cent of cases The test is also known as the Paul Bunnell test

A positive result is agglutination in serum dilution of 1 to 80 The test usual is positive after the first week of the diseas

Normal human serum, and the serum individuals who have been inoculated w horse serum, contain antibodies known Forssman antibodies, which may give positive heterophile antibody reaction is necessary therefore, to exclude false p tive reactions This is done by means of Davidsohn absorption test, which is b on the fact that Forssman antibod normal human serum is absorbed pletely by guinea pig kidney and th erophile antibody produced followin injection of horse serum is absorb guinea pig kidney and ox red bloo Since the heterophile antibodies fo the serum of patients with infectiou onucleosis is absorbed only by ox re cells false positives can thus be e Ordinarily it is not necessary to absorption tests Where doubt or

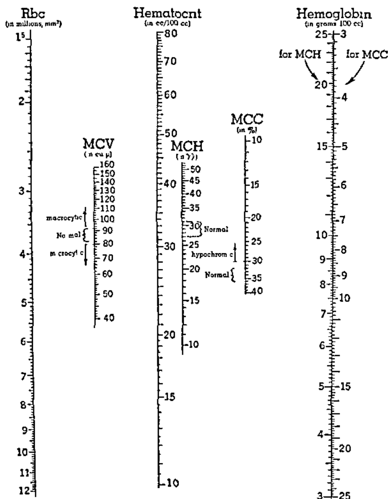


FIG 13 Nomogram for reading of corpuscular constants For M C V join the value for red cell count and hematocrit by means of a ruler The reading is made where the line intersects M C V The reading for M C H is obtained at the point where a line joining Rbc and hemoglobin intersects M C H The reading for M C H C is made where a line joining hemoglobin and hematocrit intersects M C C (From M M Wintrobe *Clinical Hematology* (ed 2) Philadelphia Lea and Febiger 1946)

exists with regard to false positives confirmation is desirable

BONE MARROW

Examination of the bone marrow is of diagnostic value in all blood dyscrasias When the peripheral blood is normal the examination is essential in suspected hematologic disease Even when the diagnosis may be established by the presence of immature forms in the peripheral blood, confirmation by means of the bone marrow aspiration is desirable Examination of the marrow is occasionally helpful in the diag

nosis of malaria It is useful in following the response to therapy, particularly in the anemias While the technic for marrow aspiration is simple, interpretation requires training and experience

The site usually selected for marrow aspiration is the midline of the sternum between the second and third ribs The skin is shaved if necessary, and an antiseptic applied An injection of 1 per cent procaine is made below the periosteum A satisfactory needle is a short beveled 16 gauge, 3 5 cm needle (B D #458) The needle is slowly introduced vertically with a boring motion until a sudden yielding sensation is felt, indicating entrance into the marrow cavity The stylet is removed and 0 5 cc of marrow fluid is withdrawn with a syringe Slight pain may be experienced on withdrawal of fluid The fluid is smeared as in a blood smear and stained with Wright s stain

The sternal puncture must be done carefully as it is not without danger Deaths have been reported due to piercing of the great vessels of the mediastinum and even of the heart Other sites for puncture have been suggested including the iliac crest and the vertebral spinous processes

Spinous Process Puncture

Aspiration of the vertebral spinous processes has been suggested recently There is little danger and less psychic trauma than with sternal puncture The lower thoracic or upper lumbar vertebrae are used An antiseptic is applied and 1 per cent procaine is injected to the periosteum The needle is introduced with a boring motion against the midportion of the spinous process just beyond the tip of the process with the needle directed forward but also somewhat upward Gentle tapping with a mallet may be necessary A yielding sensation is felt as the marrow cavity is entered The needle usually is inserted for a distance of 1 5 cm

Normal values vary widely, as given by different observers They may vary considerably in the same patient and at the same aspiration Three to five hundred white blood cells should be counted Table 64 shows normal values as given by Wintrobe The only contraindication to marrow aspiration is hemophilia

TABLE 64 *NORMAL BONE MARROW VALUES*

Cells	*Range*	*Average*
Total leukocytes	10,000–190,000 per cmm	
Myeloblasts	03 – 50	20
Promyelocytes	1.0 – 80	50
Myelocytes		
neutrophilic	5.0 – 190	120
eosinophilic	05 – 30	15
basophilic	00 – 05	03
Metamyelocytes (juvenile forms)	130 – 320	220
Polymorphonuclear		
neutrophils	70 – 300	200
eosinophils	05 – 40	20
basophils	00 – 07	02
Lymphocytes	3.0 – 170	100
Plasma cells	00 – 20	04
Monocytes	05 – 50	20
Reticuloendothelial cells	02 – 20	02
Megakaryocytes	003 – 3.0	04
Pronormoblasts	1.0 – 80	40
Normoblasts	70 – 32.0	180

SPLENIC PUNCTURE

This procedure, while simple, is dangerous and should be employed rarely The normal spleen ruptures easily, the pathologic spleen even more so Delayed hemorrhage may occur with sudden death The much less dangerous procedure of liver biopsy may yield important information which may obviate the need for splenic puncture

The procedure should not be undertaken unless the spleen is enlarged Following preparation of the skin and anesthesia with 1 per cent procaine, the patient is asked to take a deep breath and a spinal puncture needle (18 gauge) is inserted into the substance of the spleen with a short thrust Aspiration is performed

rapidly, permitting the piston of the syringe to return to its position of rest before the needle is withdrawn The patient remains in bed for twenty four hours and is observed closely for evidence of bleeding

This procedure may yield information in cases of myeloid metaplasia, other blood dyscrasias, and suspected Gaucher s disease

TOURNIQUET TEST

This is a determination of capillary fragility (the Rumpel Leede phenomenon)

A circle, 2 5 cm in diameter 4 cm below the elbow crease, is drawn on the inner aspect of the forearm Marks on the skin in this area are indicated in ink A blood pressure cuff is applied to the arm and inflated to a point midway between the systolic and diastolic pressure for a period of fifteen minutes The cuff is released and five minutes later the number of petechiae in the circle are counted

The normal is 10 or less Twenty or more is considered definitely abnormal

Increased capillary fragility may be present in scurvy, severe infections renal disease, and purpura

SICKLING METHODS

Many methods have been devised to demonstrate sickling in cases of sickle cell anemia These methods have little advantage over the following simple procedures

A drop of blood is placed on the slide which has previously been ringed with vaseline It is covered with a cover slip to exclude oxygen The slide is placed in an incubator and examined in two hours If sickling has not occurred it is again examined after a twenty four-hour period in the incubator

Moist Stasis Method

A rubber band is placed about the finger for five minutes before blood is withdrawn and examined

The sickling phenomenon is based on an abnormal molecular structure of the hemoglobin Substances which reduce hemoglobin such as sodium metabisulfite have recently been employed to advantage in the rapid detection of the sickling trait

COAGULATION TIME*

When heparin is employed in anticoagulant therapy, it is important to determine the coagulation time at frequent intervals or prior to each administration of heparin A satisfactory method for performance of the coagulation time is the Lee White method

Three Lee White tubes (Wassermann tubes 8 mm in diameter) are thoroughly cleaned and rinsed with normal saline, and thoroughly dried One cubic centimeter of venous blood is placed in each The tubes are tipped at thirty second intervals until clotting occurs The longest time observed is taken as the coagulation time

Normal value is six to fifteen minutes A control test with normal blood is desirable

With the use of heparin as an anticoagulant the coagulation time should be prolonged to a value between twenty and forty five minutes The heparin acts as an antiprothrombin and antithrombin agent Its effect may be counteracted by the use of protamine or the transfusion of fresh blood

PROTHROMBIN TIME

This is an important determination as a guide to therapy with the use of ' dicumarol as an anticoagulant The prothrombin time should be checked daily prior to the administration of each dose of dicumarol The method is based on the rate of conversion of prothrombin to thrombin when the factors of calcium and thromboplastin are kept constant The clotting time of the plasma under these

* See also Chapter 13

conditions serves as an index of prothrombin concentration

The Link-Shapiro method with undiluted plasma is satisfactory. A normal control should be used. The normal value is 13 to 17 seconds.

It is necessary to maintain the prothrombin time between 30 and 40 seconds with the use of dicumarol as an anticoagulant. Twice the normal is a fair rule. This corresponds to between 20 and 10 per cent of normal prothrombin activity. Dicumarol probably acts by inhibiting the production of prothrombin by the liver. Menadione in 60 mg. doses parenterally mitigates the effect of overdosage. The prothrombin concentration and the response of the prothrombin time to menadione is also an index of liver function and is described elsewhere.

RETICULOCYTE COUNT

The reticulocyte response is an important guide to the therapy of the anemias. It is also an index of accelerated hematopoiesis following blood loss, as in hemorrhage, or following blood destruction, as in hemolytic jaundice or sickle cell anemia.

Brilliant cresyl blue in alcoholic solution is spread on slides or cover slips and allowed to dry. A drop of blood is placed on the prepared cover slip and covered with an unprepared cover slip. In a half minute when the blood has turned deep blue-brown, the cover slips are spread apart. After drying they are counterstained with Wright's stain. With the oil immersion lens a total of 1000 red blood cells are counted and the reticulocytes noted.

The normal value is 0.5 to 1.5 per cent.

Interpretation of Results. Following the institution of liver therapy in pernicious anemia, the earliest effect is seen as an increase in the reticulocyte percentage. A response usually occurs in forty-eight hours and may reach 20 per cent in a week. In iron deficiency anemias, the response of the reticulocytes to iron appears more slowly and is not as marked. The maximum increase occurs between the fifth and tenth day. If bleeding has occurred, the maintenance of a high reticulocyte count is an indication of continued bleeding. In the *chronic hemolytic anemias*, an increase in the reticulocytes from 15–30 per cent may persist for years.

BENCE-JONES PROTEINURIA

This abnormal protein is found in two thirds of the cases of multiple myeloma. Allegedly it is found rarely in other tumors of bone, in leukemia, hyperthyroidism and empyema.

Ten cc. of urine are heated to 40° C. for a few minutes. The urine will become cloudy. At 60° C. a flocculent precipitate develops. The urine is acidified slightly with acetic acid and heated to boiling, when the precipitate will disappear. The urine is filtered while boiling. The precipitate reappears on cooling the tube.

The presence of Bence-Jones protein is indicated by a precipitate which appears at a temperature between 40 and 60° C. and disappears on boiling.

PAROXYSMAL COLD HEMOGLOBINURIA

Intravascular hemolysis in this condition is dependent on the presence in the serum of a hemolysin which is absorbed by the red blood cells only at low temperatures. Complement is not necessary for this phase but must be present for the reaction to occur on rewarming.

Ehrlich Test

Circulation to a finger is occluded with a tourniquet and the finger is immersed for a few minutes in ice water. Upon warming, local hemoglobinemia can be demonstrated.

Rosenbach Test

The hands or feet are immersed in ice water for ten to twenty minutes. Hemolysis

results if positive There may be severe constitutional symptoms

Mackenzie 'Rough' Test

A specimen of blood is chilled in ice water Hemolysis appears when the blood is warmed

Donath Landsteiner Test

A mixture of the patient s red cells, varying dilutions of his serum and guinea pig complement is immersed in ice water and then rewarmed Hemolysis is a positive test

Spectroscopic examination of the patient s urine following an episode of paroxysmal cold hemoglobinuria shows the color to be due to oxyhemoglobin methemoglobin, or hematin

COOMBS TEST FOR BLOCKING ANTIBODIES

This is a test for acquired hemolytic anemias of various types In these conditions a hyperimmune or blocking antibody combined with a specific antigen is absorbed on the surface of the red blood cells An anti human globulin serum prepared by immunizing a rabbit against human globulin is mixed with a patient s erythrocytes If rapid clumping occurs the test is positive

The Coombs test is helpful in the diagnosis of hemolytic anemias due to Rh sensitivity and other acquired hemolytic anemias The test is negative in individuals with congenital hemolytic icterus Other tests for blocking antibodies utilizing serum albumin and trypsin sensitization have been devised and are currently being evaluated

L E PHENOMENON

The L E (lupus erythematosus) cell is a polymorphonuclear leukocyte containing a large, round homogeneous inclusion body which takes basic and nuclear stains The inclusion body consists of desoxyribose nucleic acid The cell is found in clumps in most patients with active disseminated lupus erythematosus It is due to a factor which is part of the gamma globulin fraction of the plasma

The phenomenon is demonstrated by adding 1 cc of bone marrow to 0 2 mg of heparin The buffy coat is removed with a pipette and incubated for fifteen to thirty minutes The centrifuged sediment is smeared and stained with Wright s stain

Interpretation of Results The L E cell is to be differentiated from the 'tart cell which is a histiocyte containing an inclusion body which stains reddish purple with Wright s stain L E cells may also be demonstrated in peripheral blood and in normal marrow mixed with lupus erythematosus plasma The phenomenon is dependent not on an anticoagulant but only on time outside of the body for its occurrence It appears in the majority of cases of acute lupus erythematosus but only infrequently in the quiescent form of the disease A few false positives have been reported in pernicious anemia dermatitis herpetiformis and acute hemolytic anemia

Immunologic Procedures

TRICHINOSIS

Intradermal Test

Trichinella antigen (0 1 cc of the 1 10 000 solution) is injected intradermally in the flexor surface of the forearm A control of 0 1 cc of normal saline is injected in the other arm

A positive immediate reaction consists of a wheal 1 cm or more in diameter, surrounded by a zone of erythema up to sev

eral centimeters in diameter It reaches its maximum in thirty minutes Positive delayed reaction consists of redness and swelling, occurring in twenty four hours The reaction becomes positive in the second to third week of the disease and is found in 92 to 98 per cent of cases Positive reactions are usually of the immediate type There are few false positives

Precipitin Reaction

This test is less useful than the intradermal test It is specific, but may not become positive until the fifth week of the disease

Complement Fixation Test

The recent development of a new antigen for this test has made it a reliable procedure with few false positives The test becomes positive in three weeks after the onset of the disease

Persons with previous infections will have positive skin tests, precipitin reactions, and muscle biopsies long after the disease has subsided The history and clinical findings must therefore be considered in evaluating the results of these procedures

LYMPHOGRANULOMA VENEREUM

Frei Test

Chick embryo antigen (Lygranum Squibb) is employed in this valuable test

A positive reaction appears forty-eight hours after 0 1 cc of the antigen is injected intradermally The reaction consists of a small erythematous papule surrounded by a zone of erythema, the papule is 0 6 mm or more in diameter, with a control of 0 5 cm in diameter, or less Vesiculations, pustules, and necrosis may occur A maximum reaction occurs in two to three days

This test is positive in 95 per cent of cases on the seventh to tenth day after the adenopathy appears It is usually permanently positive for the life of the individual False positive Frei tests occur in the acute stage of syphilis, and chancroid atypical pneumonia psittacosis and in patients who are highly allergic If a false positive is suspected, a complement fixation test may be helpful

Complement Fixation Test

This is useful diagnostically and for the purposes of determining the effect of therapy It employs a yolk sac antigen A positive reaction is complete fixation (++++) with the unknown serum diluted to 1 6 or more, if the patient is not in the early stages of syphilis The complement fixation remains positive only as long as the virus is still present Thus the complement fixation may be used as a criterion of cure

Hyperglobulinemia a positive finding by biopsy of a lymph node, and demonstration of elementary bodies resembling those of psittacosis in the pus from a lesion are confirmatory

ECHINOCOCCUS DISEASE

Intradermal Test

An intradermal injection of 0 25 cc of sterile hydatid fluid from a known human or sheep cyst is made into the forearm A control of 0 25 cc of normal saline is used

An immediate reaction consisting of a wheal 10 mm in diameter appears in thirty minutes The delayed reaction is most significant, it occurs in eighteen to twenty four hours and consists of an area of edema and infiltration five to six cm in diameter The test often remains positive even after surgical removal of the cyst A negative test does not exclude Echinococcus disease

Complement Fixation Test

This test employs *Echinococcus* antigen and is positive in 50 per cent of cases A positive test indicates that absorption of cyst fluid is occurring and complete calcification of the cyst has not taken place

AMEBIASIS

The amebic complement fixation test is of value in hepatic amebiasis In one recent series 83 per cent of cases of hepatic amebiasis were strongly positive There were 8

per cent false positives The test is reported as 0 to ++++

The commercial antigens now available are unreliable for the diagnosis of intestinal amebiasis

BACILLARY DYSENTERY

The agglutination test has diagnostic value only in retrospect and not in relation to therapy since immune bodies seldom appear before the tenth day They reach their maximum titer after the third week of the disease when the illness has usually terminated Since normal human serum may agglutinate strains of *Shigella* in dilutions of 1 300 only a rising titer in sera taken on the tenth day and again on the twenty first day of the disease is significant Stool culture taken early in the disease is the important diagnostic measure in this disease

SALMONELLA INFECTIONS (INCLUDING TYPHOID AND PARATYPHOID FEVER)

An O agglutinin titer of more than 1 50 during the first ten days of illness is considered strong presumptive evidence of the disease if the patient has not been vaccinated within one or two years H agglutinins tend to persist for a number of years fol

Therefore the O agglutinin titer is more valuable in diagnosis Here again demonstration of a rising titer of specific agglut n ins is important evidence of definite infection with the particular *Salmonella* strain

In typhoid fever stool cultures are positive from the beginning of the disease until convalescence Blood cultures are pos tive in the first and second weeks Urine cultures are positive in the second and third week and the organisms may be excreted for a considerable period after convalescence Cultures of bone marrow may show typhoid bacilli when the blood cultures are negative Organisms may be found in the rose spots

BRUCELLOSIS

It is emphasized that a positive diagnosis can be made only by obtaining a culture of the organism

Agglutination Test

This test is of value in both acute and chronic brucellosis It usually becomes positive in a dilution of 1 40 or higher during the second week of the disease Agglutinins may disappear on recovery or may persist for years following recovery The higher the titer the more likely will be the occurrence of a positive blood culture Titers of 1 80 or higher have been obtained in 90 per cent of Brucella infections by the end of the second week

A positive agglutination test may occur as a result of an anamnestic reaction during an unrelated febrile illness Cross agglutinins are produced both by tularemia and cholera Since many individuals were vaccinated for cholera during the last war veterans may show a nonspecific high titer of brucella agglutinins The test may be negative in the presence of active disease

Intradermal Test

Spink declares that the skin test is of little value in diagnosis A positive test does not indicate active disease and a negative test does not exclude it since it is usually negative in the more serious cases of brucellosis In addition the skin test may produce agglutinins for *Brucella* in the serum in normal individuals The intradermal test therefore should be performed only after the agglutination test

Various antigens are used for the intradermal test These include heat killed cells purified protein brucellergen (nucleoprotein) and suspension of disintegrated brucella cells

Brucellergen is injected intradermally in a dose of 0 1 cc of a 1 2000 dil tion The

test is read in forty eight to seventy two hours A positive reaction is indicated by erythema, edema, and induration of at least 1 cm There may be a systemic reaction

Acute or chronic brucellosis should never be diagnosed on the basis of a positive skin test alone The main emphasis must be *placed on blood cultures* and the agglutination test If both of these are negative, a positive intradermal test must be disregarded

Opsonocytophage Test

This test is of little value

WEIL-FELIX TEST FOR RICKETTSIAL DISEASES

Epidemic and murine typhus and Rocky Mountain spotted fever produce agglutinins for *Proteus* OX 19 while scrub typhus causes a rise in titer only for *Proteus* OX K The Weil Felix reaction does not differentiate between Rocky Mountain spotted fever and the typhus fevers Q fever and rickettsial pox do not produce agglutinins for any of the *Proteus* X strains

A positive reaction for spotted fever is a titer in a dilution of 1 320 or above At least two samples of blood should be tested the first when the disease is suspected and the second during the twelfth to fifteenth day after onset A rising titer is especially significant

Typhus Fever

The Weil Felix reaction is positive early in the disease Agglutinins for *Proteus* OX 19 appear between the fifth and eighth day of the disease A positive reaction is a titer in a dilution of 1 160 or higher This may reach a peak of greater than 1 1000 in the third week of illness

Complement Fixation Test for Rickettsial Infections

This test is of value since it is highly specific and may be used to differentiate spotted fever from epidemic typhus murine typhus Q fever, scrub typhus and boutonneuse fever The complement fixation test usually remains positive for years whereas the Weil Felix reaction disappears rapidly during convalescence The complement fixation test usually becomes positive during the second week of illness Complement fixation tests may be obtained by sending specimens to the Army Medical Department, Research and Graduate School Army Medical Center, Washington 12 D C

TULAREMIA

Intradermal Test

Since this test is nearly always positive during the first week of the disease when agglutinins have not yet appeared it is a valuable diagnostic procedure

A tuberculin type reaction appears within forty-eight hours after 0 25 cc of a detoxified suspension of killed *B tularense* is injected intradermally A positive skin test persists for years following recovery from the disease Hence it is an indication of past or present infection

The intradermal injection of a minute quantity of antitularense serum causes an immediate erythematous-edematous reaction which is useful as a quick confirmatory aid

Agglutination Test

This is a reliable test and should always be used to confirm the skin test Positive titers occur during the second week of the disease but never during the first week The titer rises abruptly so that at the beginning of the third week, it is usually at a level of 1 640 or 1 1280 Since the agglutinins persist for the life of the patient a rising titer during an acute illness is of special significance Cross agglutination with *Brucella* abortus and melitensis must be excluded

49. Diagnostic Technics

II Gastroenterologic, Endocrine, Respiratory, and Miscellaneous Tests

BERNARD STRAUS

Gastrointestinal Tract

GASTRIC ANALYSIS

In the past considerable emphasis was placed on gastric analysis Greater appreciation of the wide variations which exist in normal and pathologic states has diminished the respect of the clinician for this diagnostic procedure Increasing reliance upon roentgen examinations of the gastrointestinal tract which furnishes dependable information concerning gastric motility and retention has also limited the importance of the gastric analysis Recently however with the advent of vagotomy new interest has developed in the information furnished by the gastric analysis

Fractional Analysis

With the patient fasting a Levine or Sawyer gastric tube is passed into the stomach and the fasting contents completely removed The Ewald test meal (consisting of 300 cc of water and a roll or two slices of toast without butter) is given with the optional addition of 400 cc of oatmeal gruel Ten cubic centimeter specimens of gastric content are removed at thirty minute intervals for a total of four specimens in two hours and sent to the laboratory for determination of total and free acid

Histamine Test

This procedure is performed when no free hydrochloric acid is found following the standard test meal It may be done following fasting or may be combined with the previous procedure by testing the first two specimens with four drops of Topfer s reagent If both turn yellow indicating the absence of free hydrochloric acid 0 5 cc (0 5 mg) of histamine phosphate is injected subcutaneously At thirty minutes and one hour later 10 cc specimens are withdrawn for analysis The normal values are as follows

Fasting Amount 20 to 50 cc
  Free acid under 25°
  Total acid 10 to 50°
Following a test meal
  Amount 50 to 100 cc
  Free acid 30 to 50°

Total acid 50 to 100°
After histamine (without a meal)
Amount 5 to 50 cc
Free acid 30 to 85°
Total acid 30 to 150° (in majority 80 to 130°)

The presence or absence of free hydrochloric acid following histamine stimulation or the presence of free hydrochloric acid following the test meal is the most important fact to be established as a peptic ulcer does not occur in its absence following histamine, and pernicious anemia may be excluded if it is present The value of the test is limited by the fact that true achlorhydria is present in at least 1 per cent of all normal individuals, increasing to approximately 20 per cent in individuals over 60 years of age, when gastric carcinoma is most frequent Free hydrochloric acid may be present in carcinoma of the stomach In gastric ulcer, it is frequently present in normal or diminished values The procedure of vagotomy for the treatment of peptic ulcer recently has given the test added value since the absence of free hydrochloric acid following insulin stimulation is indicative of the completeness of the vagus resection Of the various other tests of gastric content that have been suggested examination for blood with the benzidine test has occasional significance if trauma as a result of passage of the tube can be excluded

Continuous Night Secretion

This determination is employed before and after vagotomy to determine the efficacy of the operation The stomach is emptied at 9 00 P M and lavaged with an Ewald tube When returns are clear, a Levine tube is introduced through the nose and continuous suction maintained until 9 00 A M with the Wangensteen apparatus The total amount of gastric juice is measured The normal range in one study is given as 148–1188 cc with an average of 581 cc In duodenal ulcer the range was 362–1839 cc with an average of 1004 cc In gastric ulcer, the range was 202–1122 cc with an average of 623 cc The range in gastric carcinoma was 205–1243 cc with an average of 436 cc

An abnormally large continuous secretion of acid gastric juice occurs in peptic ulcer due to an increased secretory tonus in the vagus nerves It is reduced to normal by complete vagus section

Insulin Test

This test is done before and after vagotomy to determine the efficacy of the operation After vagotomy there should be no response of the gastric juice to insulin induced hypoglycemia in regard to volume, and free and total acid

After the night secretion is determined a fasting blood sugar is taken with the Levine tube in place The patient is given 5–15 units of regular insulin intravenously depending upon age weight and general condition Blood glucose levels are determined at thirty, sixty, and ninety minute intervals after injection Gastric contents are removed every thirty minutes for three hours and submitted for determination of volume free and total acid Fifty cubic centimeters of dextrose in a syringe should be on hand for administration in the event of an insulin reaction

Normally insulin hypoglycemia stimulates an increased production of acid gastric juice Failure of response to insulin hypoglycemia is indicative of complete section of the vagi following operation

Gastroscopy

This is a useful procedure in special cases It is of value in the diagnosis of gastritis and in the differential diagnosis of benign and malignant ulcers of the stomach Gastroscopy is helpful in following the course of healing of a gastric ulcer and when uncertainty exists as to the presence of gastric malignancy on examination of the gastrointestinal tract Gastroscopy also

may be helpful for the determination of operability of a neoplastic lesion

The cooperation of the patient is essential A roentgen ray examination of the gastrointestinal tract should precede examination Gastroscopy is contraindicated in the presence of disease of the esophagus deformity of the cervical or dorsal spine mediastinal disease and aneurysm of the aorta

The value of the procedure is somewhat limited by the fact that there are several blind areas of the stomach which cannot be visualized These include the pylorus frequently the lesser curvature of the antrum and the cardia a small part of the posterior wall part of the fundus above the cardia and a small area of the lower pole of the stomach Recently a flexible operating gastroscope has been devised which makes it possible to obtain biopsies of lesions in the stomach This represents a significant advance in the diagnosis of gastritis and gastric tumors

GASTROPHOTOGRAPHY

Available instruments for gastrophotography contribute little if anything which cannot be obtained by means of roentgen examination of the gastrointestinal tract and gastroscopy

INTESTINAL INTUBATION

Intestinal intubation with the Miller Abbott double lumen tube is of value chiefly as a therapeutic measure in cases of adynamic ileus and intestinal obstruction Its use has been suggested for medical ileostomy in chronic ulcerative colitis Distended intestinal loops are deflated and emptied proximal to the obstruction This renders operation safer and tends to prevent strangulation of the circulation At times it also relieves the obstruction entirely Intestinal intubation has diagnostic value in examination of intestinal juices It has been employed successfully in the localization of lesions of the small intestine following the introduction of barium through the tube It has also been of assistance in roentgenographic interpretation of motor disturbances of the small intestine

The tube is well lubricated before introduction Fluoroscopic observation is helpful When the tube reaches the midportion of the duodenum 30 cc of air are injected into the balloon and the smaller tube which is attached to the balloon is closed off Constant suction is maintained on the larger tube Passage of the tube is aided by having the patient swallow The tube usually passes through the small intestine within three to six hours although a much longer period may be required It may take one to three days before the small bowel is completely decompressed With the tube in the lower small intestine fluids may be administered by mouth If semi solid material in the intestine blocks the tube the insertion of a few ounces of warm water may dilute the contents sufficiently to permit easy passage through the tube Arrest of the progress of the tube through the intestine may be relieved by temporary deflation of the balloon Roentgenograms are of value in checking the progress of the tube The tube is readily removed by deflating the balloon and withdrawing slowly at the rate of 15 cm every five minutes

STRING TEST FOR GASTRO INTESTINAL BLEEDING

This test sometimes is useful in localizing the source of bleeding from the esophagus stomach or duodenum

Only soft white foods are eaten after breakfast on the day of the test A duodenal shot or bucket is tied to the end of a white No 5 braided silk thread 90 cm long It is marked by knotting at 55 and 80 cm from the weight At 8 00 P M the string is swallowed with the aid of milk and crackers to the 55 cm mark One hour later it is swallowed to the 80 cm mark and the

end of the string is fastened to the cheek The following morning the string is gently withdrawn while the patient drinks a glass of water If the string cannot be withdrawn without vigorous traction, it is allowed to pass through the intestinal tract

The terminal portion of the string becomes bile stained as it rests in the duodenum Blood stains in this area are indicative of bleeding from a duodenal ulcer Blood proximal to the bile stained portion indicates gastric bleeding Esophageal bleeding will stain the thread proximal to a distance of 40 cm from the teeth

Despite the advances in roentgen diagnosis this test is not obsolete Diagnosis has been established with the help of this procedure in the absence of roentgenographic findings in cases of cryptic bleeding of the upper gastrointestinal tract

ABDOMINAL PARACENTESIS

This procedure is of diagnostic and therapeutic value

The bladder is emptied—by catheterization if necessary The skin is prepared with an antiseptic and draped The site selected is usually the midline between the umbilicus and the pubis It is infiltrated with 1 per cent procaine to the peritoneum A 4 mm incision is made through the skin with the scalpel A large bore trocar is introduced into the peritoneal cavity with a boring motion A yielding sensation is felt as the trocar enters the cavity The plunger is removed and a rubber tube connected, leading to the container After the fluid is withdrawn a suture may be introduced to approximate the skin edges Collodion is not recommended A binder is applied and the patient remains in bed for the remainder of the day

The fluid is examined for specific gravity, number of cells, differential count, culture and smear, protein determination and sent for guinea pig inoculation if indicated If malignancy is suspected paraffin sections are made from the sediment of at least one liter of ascitic fluid Repeated paracentesis should be performed at different sites (not necessarily in the midline) to avoid perforation of adherent bowel

Ascitic Fluid

A transudate is usually clear in appearance It has a specific gravity below 1 018 The total protein is less than 2 5 Gm per 100 cc The fluid may contain a few endothelial cells and lymphocytes Red blood cells are rare

An exudate may be turbid or bloody It has a specific gravity of 1 018 or above The protein content is greater than 2 5 Gm per 100 cc Malignant cells have been found in the fluid of 65 per cent of patients with ascites due to neoplasm

Milky fluid necessitates the differentiation of chylous ascites due to lymphatic obstruction from pseudochylous ascites The latter is a serous type of ascites in which the effusion has undergone a physical and chemical change the nature of which is not clear In chylous ascites the fluid is milky white, containing many small fat globules A creamy layer may separate on standing The fat content may be as high as 4 Gm per 100 cc, and is chiefly cholesterol The total protein content—mainly albumin—exceeds 3 Gm per 100 cc The specific gravity is above 1 012

Pseudochylous ascites is more frequent than the chylous type It collects more slowly The appearance is milky white with an opalescent hue There is little fat and much cellular debris Total protein is less than 3 Gm per 100 cc and is predominantly due to an increase in globulin Specific gravity is less than 1 012

PROCTOSIGMOIDOSCOPY

This procedure should be part of every examination in cases of suspected colonic disorders It is essential in the diagnosis of tumors polyps strictures and ulcerations

of the lower bowel It is frequently helpful to examine scrapings from an ulcer microscopically for amebiasis and to obtain cultures Biopsy of the normal appearing rectal wall mucosa is of value in the diagnosis of schistosomiasis In the presence of macroscopic lesions of the bowel it is obviously useful Digital examination permits exploration of the terminal 8 to 10 cm of the rectum Visual examination for this distance is performed with the proctoscope With the aid of the sigmoidoscope the rectum and sigmoid can be visualized for a distance of 25 cm

The Cameron type sigmoidoscope 25 cm in length and 2×2 cm in diameter is usually employed An instrument of 1 5 cm in diameter is also satisfactory and somewhat safer for the inexperienced A saline enema of 500 cc of fluid two to four hours before the examination is desirable Patients with diarrhea or bleeding may dispense with the enema A cathartic of milk of magnesia the night before the examination, is of aid in constipated individuals A proctoscopic table is most helpful The patient is inverted with the lower extremities horizontal and abducted In the absence of a proctoscopic table the knee chest position may be used The weak and acutely ill may be examined in bed in the left lateral position with the back knees and thighs flexed The right lower extremity is flexed to a greater degree than the left Constant reassurance of the patient is necessary to achieve relaxation and cooperation Rectal examination is always performed first The warmed instrument is then well lubricated and passed beyond the internal sphincter in the direction of the umbilicus The obturator is removed and the glass shield is applied as a precautionary measure The sigmoidoscope is then advanced slowly and gently under direct vision in the direction of the promontory of the sacrum posteriorly to the middle third of the rectum It is then directed anteriorly through the rectosigmoid following the lumen of the bowel A complaint of pain is indicative of spasm The operator should stop and wait for a minute or two Patience will result in relaxation, a grateful patient, and a smooth procedure The entire attention of the operator should be devoted to the introduction of the instrument The mucosa is examined following complete insertion as the instrument is withdrawn Long cotton swabs and a suction apparatus to clear the bowel are useful A long glass pipette should be used to obtain material for microscopic examination and culture

It is important to realize that even the experienced physician cannot always pass the rectosigmoid or pass the instrument the entire 25 cm Discretion and gentleness are essential Done properly there is little pain and little danger Air inflation is usually not necessary and should be done with care In the presence of ulcerations constriction or fixation of the sigmoid special precautions must be exercised Should rupture of the bowel occur immediate laparotomy is imperative Biopsy of any tumor is an essential procedure A long shanked biopsy forceps is employed When biopsy of the rectal wall is desired the mucosa in the region of the valves of Houston is readily accessible

FECES

The value of repeated microscopic examination of fresh warm stools for *Entameba histolytica* and other parasites pus, and blood cannot be overemphasized In addition in the diarrheal diseases cultures for *Entameba histolytica, Shigella Salmonella,* and *Eberthella typhosa* infections may be indicated Examination of the stool by the zinc sulfate flotation method is valuable for cysts of *Entameba histolytica* and the tapeworms Concentration of the stool by sedimentation is indicated in suspected schistosomiasis infections The presence of occult blood in the feces is best determined by the

guaiac test Since it is less sensitive than the benzidine test a three day meat free diet is not required

FECAL FAT AND NITROGEN

In differentiating pancreatogenous steatorrhea from sprue or celiac disease, determination of the fecal fat and nitrogen is frequently necessary

The patient is placed on the standard Schmidt test diet for three days This diet consists of 118 Gm of protein, 111 Gm of fat, and 191 Gm of carbohydrate, with a total value of 2 234 calories

The diet consists of the following

Breakfast
  500 cc of milk with 50 Gm of Zwieback
Mid morning
  Oatmeal gruel (40 Gm of rolled oats)
  10 Gm of butter
  200 cc of milk
  300 cc of water
  1 egg salted to taste
Noon meal
  125 Gm of finely chopped roast beef (raw weight) lightly broiled so that the inside remains uncooked
  250 Gm of potato purée (made of 190 Gm of potato, 100 cc of milk, and 10 Gm of butter, salted to taste)
Mid afternoon
  Same as breakfast
Evening meal
  Same as mid morning

A marker is employed using 0 2 Gm of powdered charcoal in a gelatin capsule, at the beginning and end of the period under observation

Interpretation of Results Normal values on a regular diet are as follows Total fat in dry feces—7 3 to 27 6 per cent daily (average 17 5 per cent) Of this, neutral fat averages 7 3 per cent, free fatty acids, 5 6 per cent, and combined fatty acids (soaps) about 4 6 per cent Normally on the Schmidt diet over 94 per cent of the fat is absorbed so that 6 per cent or less of the dry feces is composed of fat

A total fat content amounting to more than 25 per cent of the dried feces is probably abnormal Neutral fat exceeding 11 per cent of the total fat is evidence of deficient fat splitting and occurs in pancreatogenous steatorrhea Deficient fat absorption is indicated when free and combined fatty acids exceed 16 per cent of the total dry feces and 75 per cent of the total fat This occurs in sprue

In pancreatogenous steatorrhea due to complete obstruction of the pancreatic ducts, Pratt has found 50 9 per cent of the ingested nitrogen may be recovered from the feces, while practically normal values are found in obstructive jaundice (8 per cent) and sprue (9 6 per cent) Nitrogen excretion is less than 3 Gm per day in idiopathic steatorrhea, while typically more than 3 Gm are found in pancreatogenous steatorrhea on a fat free diet Microscopic examination of the feces for undigested meat fibers is also useful

Gastric Washings Cytologic examination of the gastric washings by the Papanicolaou technic may prove to be a valuable adjunct in the diagnosis of gastric carcinoma *

RADIOLOGIC PROCEDURES†

The esophagram, the gastrointestinal series small intestinal study, the cholecystogram the barium enema with double contrast media, and mucosal studies with compression are of course, invaluable Discussion of these procedures is beyond the scope of this chapter Roentgenographic examination of the gastrointestinal tract when the patient is in the right lateral recumbent and left lateral upright position will give valuable information as to the presence of retrogastric nodes or tumor The roentgenogram is essential in cases of

* See p 1089
† See also Chapter 47

intestinal obstruction suspected ruptured viscus and in hiatus hernia

Diagnosis of Hiatus Hernia

Special maneuvers are necessary Mucosal study after a small swallow of barium may permit identification of gastric rugae above the diaphragm Examination should be done in the right oblique prone position

The Trendelenburg position may in so cases produce satisfactory filling In childr the supine position is best The junction the esophagus and stomach is at a level the seventh or eighth dorsal vertebra Som narrowing of the esophagus may be note in this location and the esophagus ma normally be somewhat dilated proximal to the area of constriction

Liver Disease

TESTS OF LIVER FUNCTION

The manifold activities of the liver are reflected in the numerous tests of its function The liver is a metabolic a digestive and an excretory organ Its great reserve capacity taxes the sensitivity of the various procedures devised to detect pathologic change That significant liver damage may be present without alteration of liver function is well known The consideration of the patient s dietary and occupational history alcoholic intake exposure to hepatic toxins previous inoculations infusions and transfusions bleeding episodes colic previous jaundice and other features are of major importance The search for spider angiomata evidence of vitamin deficiency lymphadenopathy gynecomastia gallbladder enlargement hepatosplenomegaly ascites collateral venous circulation testicular atrophy and other features is essential These elements together with macroscopic observation of the urine and feces will ield the diagnosis in a majority of cases The intelligent use of liver function tests ll increase the accuracy of diagnosis con derably Nonetheless results of tests will asionally be conflicting and the possi ty of laboratory error always exists idity in interpretation is dangerous and intelligence and experience of the ob er is the most important prerequisite

As a guide to therapy and in evaluation of therapy, tests of liver function are invalu able Of the many tests available, the most useful will be discussed

BILIRUBIN

Urine

Bilirubin is determined by the Harrison Fouchet test Bile (bilirubin bile salts, and bile acids) is found in the urine in jaundice of both hepatic and posthepatic (obstructive) origin Bilirubin may be found in the urine before jaundice appears In hemolytic jaundice bilirubin is not found unless there is secondary hepatic damage

Stools

The clay colored stool usually means absence of bile pigment and complete obstruction The color of the normal stool is due to urobilin (stercobilin) Unchanged bilirubin in the stool is found only with hypermotility of the bowel as in diarrhea A milk diet may produce a clay-colored stool or impart a light color to the stool Chemical confirmation therefore may be desirable

Schmidt s test is a simple test for bilirubin in the stool A small amount of feces is mixed with a saturated solution of mercuric chloride A green color results in six hours if bilirubin is present

Blood

Quantitative van den Bergh test This is a reliable method for the determination of the total serum bilirubin It should supplant the icterus index The normal total value is 0 1–0 8 mg per 100 cc The direct value is 0 1–0 2 mg The indirect value is 0 1–0 6 mg

A positive direct test is an indication of hepatic or posthepatic jaundice A positive indirect test alone occurs only in hemolytic jaundice Determination of the total serum bilirubin periodically is of considerable value in following the course of the jaundiced patient

UROBILINOGEN

In the Urine

Urobilinogen is a colorless chromogen formed by the reduction of bilirubin in the intestine It is partially absorbed and reconverted into bilirubin by the liver and again excreted partly in the bile and partly in the urine In complete biliary obstruction it is not formed, and hence not excreted in the stool or urine Rarely, in the presence of associated cholangitis small amounts may appear in the urine as a result of bacterial reduction of bilirubin in the finer biliary passages Hepatic damage may result in increasing failure to convert urobilinogen to bilirubin, with resultant increased amounts appearing in the urine In the hemolytic anemias urobilinogen in the urine is increased

The Wallace and Diamond method for the determination of urinary urobilinogen is roughly quantitative It must be done on a freshly voided specimen as urobilinogen is rapidly oxidized to urobilin The normal urine is positive in dilutions up to 1 20 Absence of urobilinogen and tests positive in a dilution of 1 30 or above are abnormal Absence is associated with complete obstruction either intra or posthepatic and increased values with partial obstruction hepatitis and hemolytic jaundice This is a valuable test when correlated with other findings

Normal values for the Watson quantitative method are 0 2–3 0 mg for a twenty four–hour period

In the Stool

The Watson quantitative test for urobilinogen in the stool is rarely indicated The test is complicated and difficult Normal values vary from 40 to 200 mg in twenty four hours Less than 5 mg indicates complete obstruction, and is usually associated with malignant disease Values between 5 and 40 mg per twenty four hours are indicative of partial obstruction due to calculus intrahepatic obstruction or malignant disease

Values are greatly increased in hemolytic jaundice—up to 1800 mg in twenty four hours—even though the serum bilirubin may be normal

ALKALINE PHOSPHATASE

This is a test of the excretory function of the liver Phosphatase originates in bone *and probably in the liver and other tissues* It accumulates in the blood as a result of biliary obstruction or hepatic damage

The normal values are 1 5–4 units in *adults and 5–12 units in children* (Bodansky)

Interpretation of Results Elevations of 10 units or more in jaundiced adults are *usually indicative of posthepatic* (obstructive) jaundice However, significant elevations may occur in hepatoma or metastatic carcinoma of the liver in the absence of *jaundice* In Paget s disease and other bone diseases characterized by increased osteoblastic activity, the alkaline phosphatase is also elevated Pancreatic obstruction may also produce an elevation in the alkaline phosphatase

BROMSULFALEIN TEST

This is a most useful test of hepatic insufficiency It is based on the fact that the

diseased liver is unable to remove the dye from the blood stream at a normal rate

An injection of 5 mg of the dye per Kg body weight is made intravenously Exactly 45 minutes after the injection 10 cc of blood are withdrawn from the opposite arm and the concentration of dye is determined Normally, less than 5 per cent is retained in the blood

Interpretation of Results This excretory load test determines the ability of the hepatic parenchyma to remove the dye from the blood and excrete it in the bile It is of value only in the absence of jaundice or in the presence of mild jaundice It is well adapted for following patients with chronic liver disease such as cirrhosis since usually there is no significant degree of jaundice in this condition The test is very sensitive but severe degrees of liver damage occasionally are present despite a negative test

CEPHALIN CHOLESTEROL FLOCCULATION TEST

This important test is positive in hepatic disease with or without jaundice It reflects alterations in the serum proteins due to hepatocellular damage The mechanism of the reaction is based on the fact that normally serum albumin inhibits the property of gamma globulin to produce flocculation of a cephalin cholesterol emulsion In disease a positive flocculation may be obtained with a serum if (1) there is an increase of the gamma globulin sufficient to overcome the inhibition of the albumin component (2) the serum albumin concentration is diminished (3) there is diminution in the flocculation inhibiting capacity of a normal concentration of serum albumin

Interpretation of Results The reaction reported as negative to ++++ Normally there is no flocculation of the emul n

The test is especially useful in the differ iation of posthepatic (obstructive) jaundice and hepatic jaundice, being neg in the former state It is also of value in following the progress of patients with h titis One and two plus reactions occur febrile states and other conditions The action is frequently positive in malar congestive heart failure and infectio mononucleosis

THYMOL TURBIDITY TEST

This test is useful in diffuse forms of liver disease and may be performed in the presence or absence of jaundice The reaction results from the formation of a precipitate of a globulin thymol lipid complex Both the beta and gamma globulin fractions combine with the thymol reagent

Interpretation of Results Normal values are 0 to 4 units In infectious hepatitis the thymol turbidity reaction becomes positive later and remains positive longer than the cephalin flocculation test. It is often negative in homologous serum hepatitis although the cephalin flocculation is positive False positive reactions may occur in conditions associated with hyperlipemia in rheumatoid arthritis atypical pneumonia heart failure and infectious mononucleosis

SERUM PROTEINS

Protein synthesis is dependent upon good liver function Albumin is made by the liver and diffuse liver disease results in a fall in this protein constituent The fall in serum albumin is often accompanied by a rise in globulin making the partition mandatory in suspected liver disease

Normal values are as follows Total protein 6.0–8.0 Gm per 100 cc Serum albumin 3.0–4.5 Gm per 100 cc Serum globulin 1.5–3.0 Gm per 100 cc

In cirrhosis there is first a fall in serum albumin and then with increasing severity of the process a reversal of the A G ratio In health or disease the serum albumin is

Blood

Quantitative van den Bergh test This is a reliable method for the determination of the total serum bilirubin It should supplant the icterus index The normal total value is 0 1–0 8 mg per 100 cc The direct value is 0 1–0 2 mg The indirect value is 0 1–0 6 mg

A positive direct test is an indication of hepatic or posthepatic jaundice A positive indirect test alone occurs only in hemolytic jaundice Determination of the total serum bilirubin *periodically is of considerable value in following the course of the jaundiced patient*

UROBILINOGEN

In the Urine

*Urobilinogen is a colorless chromogen formed by the reduction of bilirubin in the intestine It is partially absorbed and re*converted into bilirubin by the liver and again excreted partly in the bile and partly in the urine In complete biliary obstruc*tion it is not formed and hence not ex*creted in the stool or urine Rarely in the presence of associated cholangitis small amounts may appear in the urine as a result of bacterial reduction of bilirubin in the finer biliary passages Hepatic damage may result in increasing failure to convert urobilinogen to bilirubin with resultant increased amounts appearing in the urine In the hemolytic anemias urobilinogen in the *urine is increased*

The Wallace and Diamond method for the determination of urinary urobilinogen is roughly quantitative It must be done on a freshly voided specimen as urobilinogen is rapidly oxidized to urobilin The normal urine is positive in dilutions up to 1 20 Absence of urobilinogen and tests positive in a dilution of 1 30 or above are abnormal Absence is associated with complete obstruction either intra or posthepatic and increased values with partial obstruction hepatitis and hemolytic jaundice This is a valuable test when correlated with othe findings

Normal values for the Watson quantitative method are 0 2–3 0 mg for a twenty four-hour period

In the Stool

The Watson quantitative test for urobilinogen in the stool is rarely indicated The test is complicated and difficult Normal values vary from 40 to 200 mg in twenty four hours Less than 5 mg indicates complete obstruction and is usually associated with malignant disease Value between 5 and 40 mg per twenty four hours are indicative of partial obstruction due to calculus intrahepatic obstruction or malignant disease

Values are greatly increased in hemolytic jaundice—up to 1800 mg in twenty four hours—even though the serum bilirubin *may be normal*

ALKALINE PHOSPHATASE

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The normal values are 1 5–4 units in adults and 5–12 units in children (Bodansky)

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In cirrhosis there is first a fall in serum albumin and then with increasing severity of the process a reversal of the A G ratio *In health or disease,* the serum albumin is

almost never increased and the serum globulin hardly ever decreased

CHOLESTEROL-CHOLESTEROL ESTER PARTITION

The esterification of cholesterol is probably a function of the liver The level of total cholesterol and cholesterol esters is influenced by the liver, the thyroid the adrenal cortex, the diet, and unknown factors *Recently it has been shown that ACTH* produces a fall in cholesterol esters followed by a fall in free cholesterol probably because these constituents are utilized as a source of material for synthesis of adrenal cortical hormones

Interpretation of Results The normal values are Total cholesterol, 150–260 mg per 100 cc cholesterol esters 60–75 per cent of the total Both the total cholesterol and cholesterol esters are increased in post hepatic jaundice In jaundice due to parenchymal disease the cholesterol esters may be reduced together with a lesser decline of total cholesterol In cholangiolitic *hepatitis the total cholesterol* is increased Significant lowering of the cholesterol esters suggests a poor prognosis

GALACTOSE TOLERANCE TEST

This test of liver function depends on the efficiency of the liver to metabolize carbohydrates Galactose is a monosaccharide which is rapidly absorbed from the intestine and is utilized chiefly by the liver Its immediate utilization is independent of insulin It is indicated chiefly in the differential diagnosis of jaundice

Oral Test

The fasting patient ingests 40 Gm of galactose in 250 cc of water The urine is collected for five hours and the amount of galactose excreted is determined An excretion of 3 Gm or more of galactose is abnormal

Intravenous Test

Galactose in 50 per cent solution is injected intravenously in a dose of 0 5 Gm per Kg body weight Blood samples are obtained before and seventy five minutes after injection of galactose A value of 20 mg or more per 100 cc of blood is abnormal and suggests parenchymal disease

Interpretation of Results The galactose test is not as sensitive an indication of *hepatic disease as the bromsulfalein* test but has the advantage of being applicable to the differential diagnosis of jaundice Its value is greatest in acute hepatic injury while in chronic disease such as cirrhosis it is often negative The intravenous test is more sensitive than the oral test but adds technical difficulties In hyperthyroidism galactose is absorbed more rapidly from the intestine When 40 Gm of this sugar are given orally, a peak blood value exceeding 40 mg per 100 cc of blood is positive and indicative of hyperthyroidism The blood samples are taken at five, thirty, and sixty minutes

MENADIONE RESPONSE

In the absence of bile, vitamin K is poorly absorbed from the intestinal tract With liver damage, this vitamin is poorly utilized Either will result in a diminution in prothrombin concentration If a prolongation of prothrombin time is due simply to poor absorption, there will be a prompt fall to normal in twenty four to forty eight hours following parenteral administration of 10 mg of menadione sodium bisulfite daily for three days If it is caused by hepatic damage there will be no response

PHOSPHORUS TEST FOR HEPATIC DIABETES

Patients with disease of the liver such as hepatitis may show impaired glucose tolerance due to impairment of storage of glucose as glycogen To differentiate this condition from diabetes mellitus use is made

of the fact that with normal insulin production, there is a lowering of serum inorganic phosphorus accompanying the utilization of glucose

Glucose in a dose of 0 5 Gm per kg body weight is given intravenously over a period of thirty minutes Patients with hepatic diabetes and normal individuals experience a fall of 30 per cent of serum inorganic phosphorus at the end of the injection Patients with diabetes mellitus show a fall of less than 15 per cent

USE OF LIVER FUNCTION TESTS

In the absence of jaundice the degree of hepatic damage may be determined by the following tests of liver function the cephalin flocculation test, bromsulfalein, thymol turbidity, the serum bilirubin the alkaline phosphatase and the urine urobilinogen tests

Liver function tests of value in the differential diagnosis of jaundice include The cephalin flocculation the van den Bergh the alkaline phosphatase, serum protein partition and the urine urobilinogen It must be remembered that prolonged obstructive jaundice will produce hepatic damage which will be reflected in the tests of liver function The length of time necessary for this to occur has been stated to be six weeks However the time is exceedingly variable and is usually longer than this period

DUODENAL DRAINAGE

This procedure may afford useful information in the diagnosis of hepatic disease

With the patient fasting the duodenal tube is passed through the nose into the stomach The patient turns on his right side and the tube is slowly advanced during a fifteen to thirty minute period to the 70–85 cm mark The appearance of bile stained material indicates that the tube is in the duodenum Tincture of belladonna may be helpful in certain patients when passage of the tube is difficult The position of the tube is checked by fluoroscopy, withdrawn if kinked, and reinserted Thirty cc of 33 per cent magnesium sulfate are injected through the tube and the bile is collected

The presence of red blood cells suggest malignancy of the biliary tract, especially if bile is absent Cholesterol and calcium bilirubinate crystals indicate calculi in the gallbladder or common duct Bile stained pus cells may indicate cholangitis or cholecystitis The presence of red blood cells must be interpreted with caution, as trauma may play a role Conclusions drawn from the color or viscosity are often illusory Cultures for *E coli* or typhoid bacilli are sometimes helpful The value of this procedure is diagnostic Its therapeutic value is highly dubious

NEEDLE BIOPSY OF THE LIVER

This procedure is frequently helpful in diagnosis, as a guide to therapy, and in prognosis It may contribute to the differential diagnosis of jaundice, and is of value in hepatic involvement of obscure origin The procedure is simple, but not without danger, and should be performed only in a hospital It is contraindicated in individuals with hemorrhagic tendencies

The patient is prepared with the parenteral administration of 10 mg of menadione sodium bisulfite daily for three days When ascites is present a paracentesis is always performed first Morphine sulfate is administered in a dose of 10 mg one half hour prior to the procedure The skin is shaved, if necessary, and an antiseptic is applied After the skin is draped, 1 per cent procaine is injected into the skin subcutaneous tissue, and muscle down to the capsule of the liver A 2 mm incision is made in the skin

Abdominal Approach

If the liver is enlarged, biopsy is performed in the right epigastrium, preferably

over a nodule, or protuberance if one is felt The patient hyperventilates for ten breaths and then takes a deep breath and holds it A Vim Silverman needle is inserted cephalad at an angle of 45° into the liver just beyond the capsule The stylet is withdrawn and the bifurcated needle is inserted to its full length The outer needle is then advanced 2 cm to the flange of the inner needle A half turn is made with both inner and outer needles The bifurcated needle is then withdrawn half the length of the outer needle, and both are removed A 2 cm slice of liver tissue is usually obtained It is sent to the laboratory in 10 per cent formalin solution

Lateral Approach

If the liver is not palpable the procedure is performed through the lateral approach Following hyperventilation the patient holds his breath in expiration and the needle is inserted in the ninth or tenth interspace over an area of liver flatness in the anterior axillary line It is directed slightly ventrad and cephalad The maneuver is performed as directed in the abdominal approach

The right chest is immobilized with adhesive tape The patient remains in bed for twenty four hours The pulse is taken every half hour and the blood pressure every hour for eight hours Blood for transfusion should be readily available in the event of hemorrhage

This is a relatively safe procedure In 2 liver biopsies, the author of this chapt has had no serious accidents The reporte average mortality rate is 0 5 per cent Com plications which have occurred includ fatal hemorrhage, peritonitis bile periton tis pneumothorax, and kidney laceration

RADIOLOGIC PROCEDURES

A flat plate of the abdomen for the pre ence of radiopaque calculi within the gal bladder or within the substance of the liv is frequently desirable Calcification withi the liver may be discovered An esophagran may disclose the presence of esophage varices The esophagram should be pe formed with the Valsalva procedure (force expiration against a closed glottis) and th Mueller experiment (forced inspiratio against a closed glottis) Visualization o the gallbladder following ingestion of contrast medium is a routine procedure i suspected cholecystic disease Fluoroscopi examination of diaphragmatic movement i subdiaphragmatic abscess and amebic ab scess may be helpful Postoperative cholan giography through the T tube may deter mine the presence of remaining stones an the patency of the common duct

Pancreatic Function

SERUM AMYLASE AND LIPASE

Increase in these enzymes may occur in pancreatitis and in carcinoma of the pancreas

Serum amylase 60–180 units (Somogyi)
Serum lipase 0 2–1 5 cc of 1/20 NaOH (Cherry Crandall)

The serum amylase is elevated in acute pancreatitis for twenty four to seventy two hours It may be determined in a half hour While the serum lipase may be elevated fo a week in acute pancreatitis, it takes twenty four hours to do this determination Therefore, it is useful to perform both tests ir suspected acute pancreatitis Serum lipase is more frequently elevated in the presence of carcinoma of the pancreas than is the amylase

PANCREATIC FERMENTS IN DUODENAL FLUID

In chronic pancreatic disease and carcinoma of the pancreas information of value may be obtained by the study of the external secretion of the pancreas

A double lumen Einhorn gastroduodenal tube is passed through the nose into the duodenum to mark III (90 cm) Wangensteen suction is applied to both orifices simultaneously to remove gastric juice and duodenal fluid and thus avoid destruction of the pancreatic ferments by the hydrochloric acid of the stomach Fluoroscopy is used to check the position of the tube A specimen of pancreatic fluid is obtained before stimulation One clinical unit of secretin or 0 5 mg per kg body weight is injected intravenously to provide hormonal stimulation of the pancreas This produces a copious flow of dilute pancreatic juice which is relatively poor in ferments To produce a more concentrated fluid, richer in ferments 15 mg of acetyl β methylcholine (mecholyl) is injected subcutaneously for neural stimulation of the pancreas through the vagus nerve Either one or both of these stimulants may be employed The fluid is collected in ten minute fractions for a period of sixty minutes in a container packed in ice

Normal values with secretin (Diamond)
Volume 135–250 cc
Bicarbonate 90–130 mEq determined by titrating against 0 1 N sodium hydroxide after acidification with 10 cc of 0 1 N hydrochloric acid
Amylase 300–1200 units (Norby)
Lipase 7000–14000 units (Cherry and Crandall)
Trypsin 20–49 units (Willstater)

All values represent total output for a one hour period Since the accumulated experience with normal values has been with the methods indicated it is advisable that these methods be employed In mild or moderate chronic pancreatitis there may be a reduction in the amylase with normal or increased amounts of trypsin lipase, and bicarbonate With advanced pancreatic disease there is a reduction in all elements This is also true in obstruction of the pancreatic ducts as in carcinoma The presence of red blood cells and bile suggests ampullary carcinoma with ulceration

The gastric secretions may be measured for the presence of bile the degree of acidity, or possible change to alkalinity, to determine whether there has been regurgitation of duodenal fluid into the stomach

FECAL FAT AND NITROGEN

In pancreatic disease with extensive destruction of the acinar cells, chemical examination of the stool following the standard Schmidt diet (see p 834) will reveal an increase in the fat, nitrogen, and carbohydrates In the presence of obstructive jaundice, tests for fecal fat will be misleading because the absence of bile from the intestinal tract produces an increased secretion of fat into the intestine

GLUCOSE TOLERANCE TEST

In many instances the glucose tolerance test discloses diminished tolerance in patients with pancreatic disease In suspected hyperinsulinism, the glucose tolerance test should be carried out for a period of six hours It will show an initial rise followed by a fall to 50 mg or below, by the sixth hour A diminished response to epinephrine, with a rise of less than 35 mg per 100 cc in forty to sixty minutes may occur in hyperinsulinism due to depletion of hepatic glycogen An intravenous and oral glucose tolerance test will differentiate between pancreatogenous steatorrhea and sprue In the former, both will show diminished glucose tolerance, whereas in the latter due to impaired absorption, the oral glucose tolerance test will reveal increased tolerance with a resultant flat curve while the intravenous test will be normal or show diminished tolerance

RADIOLOGIC TECHNICS

A gastrointestinal series with study of the duodenal sweep for pancreatic enlargement and gastric displacement is frequently of value The duodenum may reveal the 'reversed 3 sign of Frostberg in carcinoma of the head of the pancreas The right lateral recumbent and left lateral upright positions are particularly useful to reveal gastric displacement due to pancreatitis or tumor of the pancreas A roentgenogram of the pancreas for calcification and lithiasis may be helpful

Metabolic and Endocrine Procedures

STANDARD GLUCOSE TOLERANCE TEST

This test is employed primarily for the diagnosis of suspected cases of diabetes mellitus It may yield significant information in thyroid disorders, hyperinsulinism, adrenal and pituitary disease Acute infections, hepatitis, and undernutrition may give false positives in the nondiabetic individual

The patient is placed on a high carbohydrate diet (300 Gm of carbohydrate minimum daily) for *at least three days prior to* the test Breakfast is omitted the patient empties his bladder, and the urine specimen is saved Five cc of venous blood are withdrawn and placed in an oxalated tube *One hundred grams of glucose (or 1 75 Gm* per Kg body weight) are given in 250 cc of water flavored with lemon juice Urine specimens and 5 cc samples of blood are collected at one half hour, one two and three hour intervals and sent to the laboratory with the fasting specimens for the determination of glucose

Interpretation of Results The fasting blood glucose is 70 to 100 mg per 100 cc During the test, it should not exceed 180 mg per 100 cc Usually it rises to a maximum of 50 mg above the fasting, and returns to normal within two hours The urine remains sugar free Where hyperinsulinism is suspected the test should be carried out for a six hour period In functional hypoglycemia or in islet cell tumors the drop in blood glucose is most marked at the end of the fifth or sixth hour

ONE-HOUR–TWO DOSE TEST (EXTON-ROSE)

This simple test is shorter and requires fewer blood samples However, it is not as reliable as the standard test It is based on the Staub Traugott effect which depends on the fact that the second of two doses of glucose produces a paradoxical reduction *in the blood glucose This may be due to* stimulation of the pancreas by the first dose of glucose with increased production of insulin The pancreas of the diabetic is unable to respond in this fashion and there *is no fall after the second dose*

After three days on a high carbohydrate diet breakfast is omitted and the bladder is emptied One hundred grams of glucose are dissolved in 650 cc of water and flavored with lemon juice It is divided into two equal parts A fasting venous blood specimen is taken and the first 50 Gm portion of the glucose solution is ingested After thirty minutes a second blood and urine specimen is obtained and the second 50 Gm portion of glucose is given One hour after the beginning of the test, the third specimens of blood and urine are obtained and all are examined for glucose

Interpretation of Results Normally, the fasting blood sugar level is 70 to 100 mg

per 100 cc The one hour level should not exceed 160 mg per 100 cc The blood glucose level is lower at the end of one hour than at the end of the first half hour All urine specimens are sugar free

A positive test reveals a fasting blood glucose which may be normal or over 120 mg per 100 cc A continued increase of more than 25 mg occurs during the second half hour The one hour blood glucose is in excess of 160 mg per 100 cc

INTRAVENOUS GLUCOSE TOLERANCE TEST

This test is employed chiefly when vomiting makes the oral standard test impracticable It is also indicated when inadequate absorption from the intestinal tract is suspected as in sprue or other deficiency states

Glucose is given intravenously in a dose of 0 5 Gm per Kg body weight as a 20 per cent solution in distilled water at a uniform rate over a period of thirty minutes Before the infusion is begun 5 cc blood samples are withdrawn for glucose determination at one half hour one hour and hourly intervals thereafter until four hours have elapsed from the time the infusion was begun

Interpretation of Results Normally the concentration of glucose in the blood does not exceed 250 mg per 100 cc upon completion of the infusion The level falls steadily thereafter going below the initial level at two hours with a return to the preinjection level or thereabouts between the third *and fourth hours*

RENAL GLYCOSURIA

This benign disorder due to failure of normal reabsorption of glucose by the renal tubules must be differentiated from diabetes mellitus

The bladder is emptied and the urine discarded A blood sample is taken and in thirty minutes a specimen of urine is obtained Thirty minutes later a second blood sample is secured

If both blood sugar values are normal and a considerable amount of glucose is found in the urine at the half hour period the diagnosis of renal glycosuria is confirmed

ALIMENTARY GLYCOSURIA

This is characterized by intermittent glycosuria following a meal due either to a lowered renal threshold for glucose or to increased permeability of the intestinal mucosa following carbohydrate ingestion The diagnosis is established by a glucose tolerance test Glycosuria appears although the blood glucose response is normal

INSULIN TOLERANCE TEST

This test is of value in the diagnosis of endocrine disorders It determines the sensitivity of the individual to insulin and the responsiveness to insulin induced hypoglycemia

The patient should be on a high carbohydrate diet for three days prior to the test. A fasting blood sample is taken One tenth of a unit of insulin per Kg of body weight is administered intravenously Blood samples are then taken in one half hour and every hour for a six hour period

Normally the blood glucose falls to about 50 per cent of the fasting level twenty to thirty minutes after injection It then rises rapidly reaching the preinjection level in ninety to one hundred twenty minutes The duration of the hypoglycemia is of greater significance than its degree

Since clinical manifestations of hypoglycemia may develop it is necessary to provide for prompt administration of glucose

Interpretation of Results Abnormality may occur in one or both of the two phases of the curve i e in the extent and duration of the hypoglycemia and in the subsequent rise toward the preinjection level

There are two important types of abnormality

1 Insulin resistance—characterized by a relatively slight (less than 50 per cent of the control level), or delayed (15 minutes or longer) fall in blood sugar Insulin resistance may be observed in primary adrenal cortical hyperfunction (Cushing s syndrome, adrenogenital syndrome) anterior pituitary hyperfunction (Cushing s syndrome or acromegaly) and in some cases of diabetes mellitus

2 Hypoglycemic unresponsiveness is characterized by undue prolongation of the period of hypoglycemia (absence of, or marked delay in the subsequent rise in blood sugar) This is observed in hyperinsulinism, Addison s disease anterior pituitary hypofunction (Simmond s disease and at times pituitary infantilism or dwarfism) and in some cases of glycogen disease This procedure may be useful in differentiating anterior pituitary hypofunction, as in Simmond s disease from anorexia nervosa and at times from primary hypothyroidism

GLUCOSE-INSULIN TOLERANCE TEST

Himsworth has proposed this test to differentiate diabetics whom he has classified as insulin resistant from those who are insulin-sensitive the latter he ascribes to insufficient production of insulin by the pancreas The insulin resistant cases occur in adrenal cortical and anterior pituitary hyperfunction as well as in diabetes mellitus

Glucose and insulin are given simultaneously as in the oral glucose tolerance test and as in the insulin tolerance test Blood samples are collected after fasting and after thirty, sixty, ninety, and one hundred twenty minutes Normally, the effect of the insulin counteracts that of the glucose, so that little or no significant change occurs in the blood sugar concentration

In diabetes due to insulin deficiency, the glucose insulin tolerance curve will be essentially normal In diabetes due to resistance to insulin, this curve will resemble the standard glucose tolerance curve in diabetes indicating relative ineffectiveness of the exogenous insulin This type of response is encountered also in some cases of acromegaly, and in Cushing s syndrome of either pituitary or adrenal origin

BASAL METABOLIC RATE

This important determination is useful chiefly in the clinical diagnosis of hypothyroidism and hyperthyroidism, and in determining the response to therapy in these conditions It is a measurement of the production of heat by the body under basal conditions as determined by the amount of oxygen consumed over a given period The oxygen consumption is measured by a spirometer By means of this determination the caloric production per square meter of body surface per hour is calculated Corrections are made for temperature and barometric pressure variations Final figures are recorded as a percentage of standard normal heat production per square meter of body surface

The patient should retire early the evening before the test No food is taken after 6 00 P M and the test is performed the following morning with the patient in the postabsorptive state for a period of twelve to sixteen hours *If possible, it is preferable* that the test be done in the patient's own room If transportation is necessary, it is desirable that the patient should rest quietly for an hour after he has reached the basal metabolism room Smoking is interdicted and every effort is made to avoid excitement or anxiety

The apparatus usually employed is of the Benedict Roth type The patient breathes through a closely fitting soft rubber mouth piece with the nose closed by rubber clamp The spirometer bell is filled with oxygen The patient inspires the oxygen through

the bell and, by means of a valve, the inspired air passes through a soda lime chamber where the carbon dioxide is removed and the remaining oxygen is returned to the bell of the spirometer The amount and rate of oxygen consumed is recorded on a revolving drum The volume of oxygen utilized over a six minute period is readily calculated The level of the spirometer bell at the beginning and at the end of the test period is indicated by drawing a straight line touching the bottom of the greatest number of respiratory deflections The difference between these two levels yields the amount of oxygen consumed in terms of calories per hour

It is desirable to have the patient breathe room air through the apparatus for a few minutes until the initial apprehension is allayed If the respirations are irregular or uneven, as indicated by the recorded waves the test should be repeated It is important to test for leaks in the apparatus The calculation of surface area is made from the height and weight of the patient and corrections are made of the oxygen consumption for temperature and barometric pressure with the aid of standard charts

Interpretation of Results Normal values vary from +15 to −10 per cent of the normal standard oxygen utilization

The basal metabolic rate is increased in hyperthyroidism emotional disturbances fever, leukemia severe anemia polycythemia hyperpituitarism diabetes mellitus cardiac decompensation and occasionally in pregnancy In hypothyroidism it is usually more than +30

While the majority of cases of hyperthyroidism are readily diagnosed borderline cases may present considerable difficulty Various procedures, in addition to the basal metabolic rate, have been proposed to aid in the diagnosis of these cases Very useful is the response to iodine administration Institution of iodine therapy produces a prompt subjective improvement and a fall in basal metabolic rate which is diagnostic Iodine is preferable to propylthiouracil in this regard as it acts more promptly Propylthiouracil is also less desirable because it produces lowering of the basal metabolic rate in the absence of hyperthyroidism while iodine does not Diminution in the serum cholesterol usually is not marked enough to be helpful Elevation in the serum precipitable iodine above 16 micrograms is significant but the determination is difficult and is performed by few laboratories Evidence of hepatic damage or rapid glycogenolysis as indicated by impaired glucose or galactose tolerance is contributory evidence An increase in the uptake of radioactive iodine by the overactive thyroid is important Creatinuria and decrease of creatinine retention following a test dose have been shown to be too variable to be of much diagnostic value

The basal metabolic rate is diminished in hypothyroidism, thyroiditis, nephrosis, hypopituitarism Addison's disease, undernutrition, and shock In hypothyroidism it is usually below −15 A diagnosis of primary hypothyroidism in patients in whom the basal metabolic rate is more than 20 per cent below normal in the absence of edema is considered questionable In the obese values which are somewhat below normal must not be misinterpreted as a sign of hypothyroidism Adipose tissue is less active metabolically and may introduce an error because of the effect of the body surface area

The importance of close attention to detail to insure having the patient in the basal state cannot be overemphasized If the test is done by a technician every step of the procedure must be carefully checked

RADIOACTIVE IODINE MEASUREMENT OF THYROID FUNCTION

The uptake of I^{131} by the thyroid is a valuable test of thyroid activity Approx

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2 Hypoglycemic unresponsiveness is characterized by undue prolongation of the period of hypoglycemia (absence of, or marked delay in the subsequent rise in blood sugar) This is observed in hyperinsulinism, Addison's disease, anterior pituitary hypofunction (Simmond's disease and at times pituitary infantilism or dwarfism), and in some cases of glycogen disease This procedure may be useful in differentiating anterior pituitary hypofunction, as in Simmond's disease, from anorexia nervosa and at times from primary hypothyroidism

GLUCOSE-INSULIN TOLERANCE TEST

Himsworth has proposed this test to differentiate diabetics whom he has classified as insulin resistant from those who are insulin sensitive, the latter he ascribes to insufficient production of insulin by the pancreas The insulin resistant cases occur in adrenal cortical and anterior pituitary hyperfunction as well as in diabetes mellitus

Glucose and insulin are given simultaneously, as in the oral glucose tolerance test, and as in the insulin tolerance test Blood samples are collected after fasting and after thirty, sixty, ninety, and one hundred twenty minutes Normally, the effect of the insulin counteracts that of the glucose, so that little or no significant change occurs in the blood sugar concentration

In diabetes due to insulin deficiency, the glucose-insulin tolerance curve will be essentially normal. In diabetes due to resistance to insulin, this curve will resemble the standard glucose tolerance curve in diabetes, indicating relative ineffectiveness of the exogenous insulin This type of response is encountered also in some cases of acromegaly, and in Cushing's syndrome of either pituitary or adrenal origin

BASAL METABOLIC RATE

This important determination is useful chiefly in the clinical diagnosis of hypothyroidism and hyperthyroidism, and in determining the response to therapy in these conditions It is a measurement of the production of heat by the body under basal conditions as determined by the amount of oxygen consumed over a given period The oxygen consumption is measured by a spirometer By means of this determination the caloric production per square meter of body surface per hour is calculated. Corrections are made for temperature and barometric pressure variations Final figures are recorded as a percentage of standard normal heat production per square meter of body surface.

The patient should retire early the evening before the test No food is taken after 6 00 P M and the test is performed the following morning with the patient in the postabsorptive state for a period of twelve to sixteen hours *If possible, it is preferable* that the test be done in the patient's own room If transportation is necessary, it is desirable that the patient should rest quietly for an hour after he has reached the basal metabolism room Smoking is interdicted and every effort is made to avoid excitement or anxiety

The apparatus usually employed is of the Benedict Roth type The patient breathes through a closely fitting soft rubber mouth piece with the nose closed by rubber clamp The spirometer bell is filled with oxygen The patient inspires the oxygen through

the bell and, by means of a valve, the inspired air passes through a soda lime chamber where the carbon dioxide is removed and the remaining oxygen is returned to the bell of the spirometer The amount and rate of oxygen consumed is recorded on a revolving drum The volume of oxygen utilized over a six minute period is readily calculated The level of the spirometer bell at the beginning and at the end of the test period is indicated by drawing a straight line touching the bottom of the greatest number of respiratory deflections The difference between these two levels yields the amount of oxygen consumed in terms of calories per hour

It is desirable to have the patient breathe room air through the apparatus for a few minutes until the initial apprehension is allayed If the respirations are irregular or uneven, as indicated by the recorded waves, the test should be repeated It is important to test for leaks in the apparatus The calculation of surface area is made from the height and weight of the patient and corrections are made of the oxygen consumption for temperature and barometric pressure with the aid of standard charts

Interpretation of Results Normal values vary from +15 to −10 per cent of the normal standard oxygen utilization

The basal metabolic rate is increased in hyperthyroidism emotional disturbances fever leukemia severe anemia polycythemia hyperpituitarism diabetes mellitus, cardiac decompensation and occasionally in pregnancy In hypothyroidism it is usually more than +30

While the majority of cases of hyperthyroidism are readily diagnosed borderline cases may present considerable difficulty Various procedures, in addition to the basal metabolic rate, have been proposed to aid in the diagnosis of these cases Very useful is the response to iodine administration Institution of iodine therapy produces a prompt subjective improvement and a fall in basal metabolic rate which is diagnostic Iodine is preferable to propylthiouracil in this regard as it acts more promptly Propylthiouracil is also less desirable because it produces lowering of the basal metabolic rate in the absence of hyperthyroidism while iodine does not Diminution in the serum cholesterol usually is not marked enough to be helpful Elevation in the serum precipitable iodine above 16 micrograms is significant but the determination is difficult and is performed by few laboratories Evidence of hepatic damage or rapid glycogenolysis as indicated by impaired glucose or galactose tolerance is contributory evidence An increase in the uptake of radioactive iodine by the overactive thyroid is important Creatinuria and decrease of creatinine retention following a test dose have been shown to be too variable to be of much diagnostic value

The basal metabolic rate is diminished in hypothyroidism, thyroiditis, nephrosis hypopituitarism, Addison s disease undernutrition, and shock In hypothyroidism it is usually below −15 A diagnosis of primary hypothyroidism in patients in whom the basal metabolic rate is more than 20 per cent below normal in the absence of edema is considered questionable In the obese values which are somewhat below normal must not be misinterpreted as a sign of hypothyroidism Adipose tissue is less active metabolically and may introduce an error because of the effect of the body surface area

The importance of close attention to detail to insure having the patient in the basal state cannot be overemphasized If the test is done by a technician every step of the procedure must be carefully checked

RADIOACTIVE IODINE MEASUREMENT OF THYROID FUNCTION

The uptake of I^{131} by the thyroid is a valuable test of thyroid activity Approx

imately 25 μc of I^{131} are administered orally and the amount taken up by the thyroid gland is measured with a Geiger counter after twenty four hours Normal values in euthyroid subjects range from 10 to 50 per cent The uptake in patients with hyper *thyroidism is above 50 per cent In myx* edema or thyroiditis the values are below 10 per cent The test cannot be performed on patients who have recently been given iodine

It has recently been suggested that deter mination of I^{131} clearance from the blood is a more reliable index of the iodine accu mulating function of the thyroid gland than the twenty four hour I^{131} uptake The thyroidal plasma I^{131} clearance is the vol ume of plasma cleared of I^{131} per minute by the thyroid gland The range of thyroid clearance values in normal subjects is 8–40 cc /min/1 73 m ^{2} surface area (Berson and Yalow)

Adrenal Function

DISORDERS involving alteration in adre nal function are often suspected on clinical grounds alone Few conditions in medicine are as spectacular as the advanced case of Addison's disease or Cushing s syndrome However, a host of conditions varying from neurasthenia to polycythemia may sim ulate diseases of the adrenal glands A clinical diagnosis of Addison s disease or Cushing's syndrome must always be con sidered a tentative one until confirmed by laboratory means Our resources in many cases are taxed to the utmost to arrive at the correct conclusion In the absence of crisis or overt manifestations of disease, there may be no significant changes in the serum electrolytes Alterations in glucose tolerance in either direction may be mini mal The basal metabolic rate, blood count, and roentgen study of the adrenal often add little Recourse to more elaborate stu dies of adrenal function must then be had While all the procedures described here are not necessary in most cases they are all useful and are valuable in particular prob lems involving dysfunction of the adrenal glands

ROBINSON KEPLER-POWER TEST

Procedure I Water Test

This test is based on the volume of urine excreted following the ingestion of a large amount of water It is dependent upon the fact that patients with Addison s disease do not usually experience normal diuresis The urine remains concentrated even after copious water drinking The excretion of water is delayed

On the day before the test the patient eats three ordinary meals but omits extra salt He is requested not to eat or drink anything after 6 00 P M Until this time he may drink water as desired At 10 30 P M he empties his bladder and discards the urine All urine which is voided from then on until 7 30 A M is collected The volume of this urine is measured and saved for chemical analysis, if this should be neces sary later Breakfast is omitted The patient is asked to void again at 8 30 A M and im mediately thereafter he is given 20 cc of water per kg body weight He is asked to drink this within the next forty five min utes At 9 30, 10 30 11 30 A M and 12 30 P M he is requested to empty his bladder To eliminate the effects of exercise and posture on urinary excretion he is kept at rest in bed except when necessary to void Each specimen is kept in a separate con tainer The volume of the largest of these four specimens is recorded

Some patients with Addison s disease will excrete so little urine that they are unable to void more than once or twice during the

entire morning In such instances the amount of urine excreted per hour may be calculated Frequently however, such cal culations are unnecessary because of the low urinary output throughout the entire morning

If the volume of any single hourly speci men voided during the morning is greater than the volume of night urine, the re sponse to the test is negative Such a response indicates the absence of Addison s disease If the volume of the largest hourly specimen voided during the morning is less than the volume of urine voided during the night the response to the test is posi tive indicating Addison s disease may or may not be present To establish the diag nosis Procedure II should then be insti tuted

Procedure II

This test is based on the fact that patients suffering from Addison s disease tend to excrete excessive amounts of sodium chloride, but retain urea

A fasting blood specimen is analyzed for urea nitrogen and chloride The night urine is also analyzed for urea nitrogen and chloride and the following equation is solved

$$A = \frac{\textit{Urea N in night urine}\ (\text{mg}/100\ \text{cc})}{\textit{Urea N in serum}\ (\text{mg}/100\ \text{cc})} \times \frac{\textit{Cl in serum}\ (\text{mg}/100\ \text{cc})}{\textit{Cl in urine}\ (\text{mg}/100\ \text{cc})} \times \frac{\textit{Vol day urine}\ (\text{cc})}{\textit{Vol night urine}\ (\text{cc})}$$

Where day urine=largest of hourly specimens during day

Where night urine=entire amount voided from 10 30 P M to 7 30 A M

If the value of *A* in this equation is greater than 30 the patient probably does not have Addison s disease If the value of *A* is less than 25 the patient probably has Addison s disease, provided that nephritis has been excluded

SALT DEPRIVATION TEST

The patient is placed on a diet contain ing 1 5 Gm of sodium chloride and ap proximately 4 Gm of potassium per day On the first and second day of the test, 1 cc. of 10 per cent potassium citrate per kg body weight is given Before beginning the test the patient is weighed the basal blood pressure is taken, and initial serum sodium, serum chloride, and hematocrit values are determined On the first and second day of the test 40 cc of water per kg body weight is given On the third day of the test, 20 cc. of water per Kg is administered prior to 11 00 A M The important urine examina tion for analysis is that collected from 7 00 A M to 11 00 A M on the third day of the test This specimen is analyzed for sodium and chloride concentration In addition it is important to follow the body weight, blood pressure, the serum sodium, serum chloride, and hematocrit throughout the test A sudden reduction in blood pressure or clinical symptoms of marked dehydration are danger signals following which the test should be discontinued immediately, and the patient given sodium chloride infusion intravenously and adrenal cortical extract

Addison s disease can be excluded if the concentration of sodium and chloride in the four hour specimen on the third day of the test is below 100 mg per 100 cc. for sodium and 150 mg per 100 cc for chloride, or if there has been no significant change in the clinical condition of the patient throughout the test This test is not without danger, and should be performed under careful supervision

ADRENOCORTICOTROPIC HORMONE (CORTICOTROPIN) TEST

Following the administration of adreno corticotropic hormone there is normally a rather prompt fall in the number of circu lating eosinophils and a rise in the uric acid–creatinine ratio in the urine These effects are negligible or absent in the pa tient with Addison's disease

On the day prior to the test food is with held from the patient after 8 00 P M At 6 00, 8 00 and 10 00 A M the following day,

the patient is given 200 cc of water by mouth The control urine consists of the urine excreted from 6 00 to 8 00 A M A control eosinophil count is done at 8 00 A M following which 25 mg of adreno corticotropic hormone is given intramuscularly The urine from 9 00 A M to 12 00 noon is collected and the eosinophil count is repeated at noon The uric acid and creatinine content in each of the two urine specimens are determined and the rise in uric acid creatinine ratio calculated

Eosinophil Count

Oxalated blood is drawn into a white cell count pipette to the 0 5 mark The pipette is then filled with a diluting fluid made up of 5 cc. of 2 per cent eosin solution in water 5 cc of acetone, and distilled water sufficient to make 100 cc The pipette is shaken for 30 seconds the counting chambers filled and the eosinophils are counted Eosinophils appear bright red against a pink background The other leukocytes are colorless The count should be made promptly after dilution has been accomplished The average count in four large squares multiplied by 6 25 gives the number of eosinophils per cubic centimeter The decrease in eosinophils is expressed as the percentage of the initial count

Interpretation of Results The fall in eosinophils and rise in uric acid excretion reach their maxima in about four hours A reduction of 50 per cent or more in the eosinophil count and an increase of 50 per cent or more in the uric acid–creatinine ratio during the test is presumptive evidence that the adrenal cortex has normal capacity to respond to stimulation The effect on the eosinophil count is the more sensitive of the two tests A fall in the eosinophil count of 50 per cent or more is good evidence that Addison s disease may be excluded It reflects increased secretion of 11 17 oxysteroids and measures the capacity of the adrenal gland to respond to further stimulation An increase of less than 50 per cent in the uric acid–creatinine ratio is indicative of Addison s disease

FORTY EIGHT-HOUR 17 KETO STEROID RESPONSE

ACTH administration produces an increased urinary 17 ketosteroid excretion and indicates more directly the degree of adrenocortical stimulation It may be combined with the four hour test

Following the administration of 25 mg of ACTH in the four hour test 10 mg of ACTH is given every six hours during the subsequent forty-eight-hour period Excretion of 17 ketosteroids is measured prior to ACTH administration and during the twenty four– to forty eight–hour period on ACTH

The normal increase in adults is approximately 4–8 mg per day

EPINEPHRINE TEST

Epinephrine is believed to stimulate the anterior pituitary gland to secrete ACTH which in turn stimulates the adrenal cortex

Breakfast is withheld and a fasting eosinophil count is done Epinephrine hydrochloride (0 3 cc of 1 1000 solution) is injected subcutaneously The patient may then eat Four hours later a second eosinophil count is done

A normal response is a fall of 50 per cent or more in circulating eosinophils Patients with pituitary or adrenal insufficiency show little or no response

Fasting Eosinophil Count

The normal total eosinophil count is 100–250 cells per cc Less than 50 cells suggests adrenal cortical hyperfunction (Cushing s syndrome)

17 KETOSTEROID EXCRETION IN URINE

The 17 ketosteroids are excretion products of certain adrenal steroids and of

testosterone Hence they are an index of the combined activity of the adrenal cortex and the interstitial tissue of the testis in the male and of the adrenal cortex alone in the female In the male, two thirds of the total ketosteroids are due to adrenal cortical activity Normal values are as follows

Total neutral 17 ketosteroids
men 7–20 mg per twenty four hours
women 5–15 mg per twenty four hours
Alpha and beta ketonic fractions
85–90 per cent of total of which the beta fraction is 5 per cent or less
Nonketonic fraction
10–15 per cent of total

The 17 ketosteroids are primarily an index of adrenal cortical function Since both the adrenal cortex and the testis are under the influence of the pituitary, the 17 ketosteroids are also an indication of pituitary function High values are seen in adrenal cortical carcinoma and hyperplasia The beta ketonic fraction is particularly elevated in adrenal cortical carcinoma Low values are seen in Addison s disease, Simmond s disease, anorexia nervosa and myxedema

11 OXY CORTICOSTEROIDS

A colorimetric test is used to measure the cortical hormones having a glycogenic action The results are similar to and parallel the glycogenic corticoid determinations by biologic test The normal value is 0 1–0 44 mg per twenty four hour specimen of urine

Low values are found in Addison s disease, hypopituitarism and myxedema High values occur in Cushing s syndrome

CHORIONIC GONADOTROPIN

This is determined by the familiar pregnancy test for which the Friedman modification of the Aschheim Zondek test is most satisfactory

Ten to fifteen cubic centimeters of fresh urine is injected intravenously into the ear vein of a nonpregnant rabbit weighing not less than four pounds The ovaries of the animal are examined twenty four hours later

A positive test demonstrates the presence of corpora hemorrhagica, or corpora lutea

QUANTITATIVE ASCHHEIM-ZONDEK TEST

This test is useful in the diagnosis of such tumors as hydatidiform mole, chorionepithelioma embryonal carcinoma, seminoma and teratoma

The urine is diluted 1 10 1 50, 1 100 and 1 1 000 Of these diluted urines and of undiluted urine, 0 5 cc is injected subcutaneously into each of 5 immature female white mice 21–30 days old, weighing 6–8 Gm The animals are killed ninety six to one hundred hours later and the ovaries examined

If the 1 10 dilution is positive, not less than 3330 mouse units of hormone per liter of urine are present Correspondingly higher concentrations are present if the higher dilutions are positive

In males with seminoma and teratoma of the testis less than 3330 mouse units of hormone per liter may be present In these cases concentration methods must be employed on the urine Highest titers are found in chorionepithelioma and hydatidiform mole

FOLLICLE STIMULATING HORMONE

Excretion of FSH in the urine is measured by bioassay (Klinefelter) It gives some indication of pituitary function The normal value is 6 6–53 mouse units per twenty four hours

FSH is elevated in ovarian aplasia in the male and female climacteric, and in eunuchoidism Low levels are found in Simmond s disease, anorexia nervosa and pituitary infantilism

ESTROGENS

A fluorometric test has recently been devised which may prove to be simple and

useful It is an index of the function of the ovarian follicle

PROGESTERONE

This is measured by determination of pregnandiol its excretion product in the urine

SULKOWITCH TEST

This is a test for calcium excretion in the urine Since it gives an approximation of the serum calcium concentration it is particularly useful as a guide for therapy in patients who are receiving dihydro tachysterol or parathormone

Sulkowitch s reagent (1 7 per cent oxalic acid 1 7 per cent ammonium oxalate and 3 3 per cent glacial acetic acid in water) and urine are mixed in equal amounts If no precipitate of calcium oxalate appears the serum calcium is 5–7 5 mg per 100 cc If there is a fine precipitate the serum calcium concentration is within normal range If there is a heavy milky precipitate there is hypercalcemia

This test is fairly crude and does not supplant the serum calcium determination It is useful chiefly as a daily guide in the control of therapy in patients with hypo parathyroidism

URINARY CALCIUM EXCRETION TEST

In mild cases of hyperparathyroidism determination of urinary calcium excretion is of aid in diagnosis

The patient is placed on a low calcium diet containing 125 mg of calcium daily for one week A twenty four–hour urine collection is made at the end of the week A calcium excretion of 150 mg or more is *positive and* suggests hyperparathyro dism

CARBOHYDRATE METABOLISM INDEX (CMI) FOR THIAMIN DE FICIENCY (HORWITT AND KREISLER)

This test is based upon the abnormal metabolism of pyruvic acid which occurs in *thiamin deficiency Glucose and* exercise are used to provide a double metabolic load on the mechanism of carbohydrate utilization

A fasting blood sample is obtained and 9 cc of 20 per cent glucose per Kg body weight is given orally One hour later the patient walks a flight of 21 steps 19 cm high up and down for 60 seconds Another blood sample is obtained 5 minutes later The CMI is calculated by the following *formula*

$$CMI = \frac{L - \frac{G}{10} + 15P - \frac{G}{10}}{2}$$

G I and *P* are the levels of glucose lactic acid and pyruvic acid in mg per 100 cc of blood

The upper limit of the normal CMI is 15 Values above 15 are indicative of thiamin deficiency The shortcoming of the basal lactic and pyruvic acid levels as a criterion of thiamin deficiency is the large individual variations This is believed obviated by the load test

ASCORBIC ACID SATURATION TEST

Wide normal fluctuations in the vitamin C content of the plasma and the vitamin C excretion in the urine necessitate a more sensitive test for vitamin C deficiency

One gram of ascorbic acid is injected in travenously The urine is collected for five hours and the ascorbic acid excretion deter mined

A positive test indicating a deficiency of vitamin C is an excretion of less than 0 4 Gm If there is no undersaturation of the tissues with ascorbic acid a greater amount will be excreted This procedure is em ployed to confirm the Rumpel Leede s test for capillary permeability

RADIOLOGIC PROCEDURES IN ENDOCRINE DISORDERS

The bone survey including skull chest long bones hands pelvis and spine is of great value A flat plate of the abdomen

for renal or adrenal calcification and a pyelogram for renal calculi are useful Measurement of the size of the sella turcica *is often important* The upper limits of normal of the adult sella turcica measured by roentgenogram as given by different workers are 10–12 mm in depth and 12–16 mm in length

Perirenal Insufflation of Air

This procedure, when combined with laminography, is useful for the diagnosis of adrenal tumors and adrenal hypertrophy

With the patient lying on his side a spinal needle is inserted below the twelfth rib, just anterior to the sacrospinalis muscles The needle is directed slightly upward through the subcutaneous fat and the muscles Resistance is encountered at the transversalis fascia following which the needle enters the soft perirenal fat The needle is aspirated to be sure that it is not in a blood vessel and then 400 cc of air or oxygen are injected slowly by means of a pneumothorax machine The injection should take thirty minutes The opposite side may then be injected similarly Laminograms are made in the anteroposterior view at levels of 7 8, and 9 cm above the table top in adults In children or thin adults exposures are made at 4, 5, or 6 cm

Laminography has improved the reliability of this procedure but results must be interpreted cautiously Hazards are shock, hemorrhage, and air embolism

Pulmonary Disease

SPUTUM STUDIES FOR TUBERCULOSIS

Careful instruction of the patient in order to obtain a good sputum is imperative Nasal secretions or saliva are useless Casual specimens are generally unsatisfactory and are employed only if haste is imperative Twenty four–hour specimens of bronchial secretion should be obtained Material is smeared directly and concentrations are done if the direct smear is negative A second twenty four–hour sputum should always be obtained whether the first is positive or negative for purposes of confirmation If the first two sputa are negative, it is desirable to obtain seventy two–hour concentrates usually three in number If these are negative cultures of tubercle bacilli are made from the sputum If the patient is to be treated with streptomycin it is desirable to culture positive sputa in order to perform sensitivity studies If the sputum concentrates and cultures are negative a seven day collection of sputum may be indicated

GASTRIC WASHINGS

When no sputum is brought up or the sputum is inadequate, it is desirable to obtain cultures of gastric washings Usually three cultures are obtained

For best results gastric washings should be obtained early in the morning, shortly after the patient awakens, with the patient fasting A Levine tube is passed into the stomach and the gastric content is aspirated If no gastric content is obtained, the patient may drink a half glass of water and aspiration is attempted after fifteen minutes Since exposure to acid gastric content for several hours interferes with growth of tubercle bacilli, specimens should be neutralized after withdrawal This is done by *the addition of sodium bicarbonate solution* until the specimen is alkaline to litmus paper, or a quantity of 23 per cent tribasic sodium phosphate equal to the washing may be added Cultures rather than smears should be made of the gastric content, since the latter are rarely helpful

In a proved case of tuberculosis, smears of single monthly seventy-two-hour concentrates of the sputum are done where the previous positive has been found on smear If the previous positive has been on culture, follow up studies should be cultured

In 20 per cent to 30 per cent of patients with minimal asymptomatic tuberculosis, tubercle bacilli cannot be demonstrated Repeated gastric washings in the first two months are undesirable, unless there is clinical or roentgenologic evidence of progression

When acid fast bacilli have been found on smear or culture, occasionally it may be necessary to determine pathogenicity In this situation and occasionally as a check when cultures have been negative, a guinea pig inoculation may be performed

Disappearance of tubercle bacilli from previously positive secretions suggests that the process has become arrested

Gaffky counts for quantitative grading of sputa are undesirable as they are inaccurate Fluctuations in the number of tubercle bacilli are frequent and have no prognostic significance unless they are marked and maintained during many examinations over the course of several months

Pinner has stated that 60–70 per cent of tuberculous patients will produce positive smears, including concentrates, and an additional 30–40 per cent will be found positive if cultures of sputum and gastric contents are done Between 60–70 per cent of the patients in whom tuberculosis is diagnosed will be found positive by one of the first three sputum examinations

ANIMAL INOCULATION FOR DIAGNOSIS

Guinea pig inoculations are necessary in rare cases when all other methods have failed. It is also sometimes necessary to differentiate acid fast bacilli which are pathogenic from acid fast saprophytes Differentiation of tubercle bacilli into human bovine, and avian strains must be confirmed by their differential pathogenicity for guinea pigs, rabbits and fowl

AMYLOIDOSIS

The Congo red test is a useful test for secondary amyloidosis An intravenous injection of 0 25 cc of 1 per cent Congo red solution per kg body weight is made Four minutes later, 10 cc of blood are removed from a vein in the opposite arm and placed in a labeled oxalated tube One hour after the injection of dye a second 10 cc sample of blood is obtained and labeled, and both are sent to the laboratory

Interpretation of Results A positive test for amyloidosis is indicated by the disappearance of 90–100 per cent of the dye from the blood at the end of one hour A normal plasma protein concentration, especially albumin, is required to hold the dye in the blood stream In the nephrotic syndrome, the dye tends to disappear rapidly from the blood, appearing in the urine adsorbed to albumin Usually 40–60 per cent of the dye disappears from the blood in one hour in the nephrotic syndrome The minimum time for the accumulation of sufficient amyloid to give a positive reaction is considered to be nine months with an average of one and a half to two years False negatives as well as false positives are occasionally observed and it is well to repeat the test for confirmation A liver biopsy may be employed to obtain tissue for staining as a confirmatory test in doubtful cases

In primary amyloidosis the Congo red test is frequently negative Hence, biopsies of the tongue, skin or ear lobe are necessary These should be stained after fixation, with iodine, Congo red and such metachromatic dyes as methyl violet

THORACENTESIS

Fluid is localized by physical examination, fluoroscopy, or the roentgenogram The patient is in the sitting position if possible If he is too ill, the supine position is satisfactory After preparation of the skin with antiseptic solution, 1 per cent procaine is introduced to the pleura An 18 gauge needle is introduced into the pleural space, attached to a three way stop cock in order to prevent air from entering the space The needle should be withdrawn completely if a dry tap is encountered and re introduced to avoid traumatizing tissue Ordinarily not more than 750 cc of fluid should be removed at a sitting

Fluid is examined for specific gravity cell, and differential count total protein and smear and culture, if indicated If a neoplasm is suspected the entire amount withdrawn should be sent to the laboratory for centrifugation and fixation Transudates are differentiated from exudates as described under ascitic fluid

BRONCHOPLEURAL FISTULA

The following methods are useful in the diagnosis of bronchopleural fistula

Methylene Blue Test

If fluid as well as air is present in the pleural space, 10 cc of sterile, 1 per cent solution of methylene blue is injected Blue stained sputum will be expectorated within a few hours or a few days dependent upon the size of the fistula

Pressure Test

The intrapleural pressure is measured with a pneumothorax apparatus Air is withdrawn and the pressure decreases If the pressure returns to that existing before the withdrawal of air within a few minutes a fistula is present

Gas Analysis

In the presence of a bronchopleural fistula the gas in the pleural space is mixed with alveolar air and therefore its oxygen content is higher than in a closed pneumothorax, and its carbon dioxide content is less A concentration of carbon dioxide less than 5 per cent and of oxygen of more than 7 per cent is diagnostic of bronchopleural fistula If a pleural effusion exists, however, the carbon dioxide is usually more than 9 per cent and the oxygen less than 0 25 per cent in a closed pneumothorax Therefore, a bronchopleural fistula should be diagnosed in the presence of an effusion when an oxygen content of more than 1 per cent is found Gas analysis for bronchopleural fistula is performed only when the first two tests have failed

TOPICAL ANESTHESIA FOR LARYNGOSCOPY AND BRONCHOGRAPHY

Indirect laryngoscopy ordinarily does not require a local anesthetic In apprehensive and sensitive patients local anesthesia is necessary Topical anesthesia is always required for bronchography

Pentobarbital, 0 1–0 2 Gm is given orally two hours prior to the procedure Food is withheld for four hours prior to induction of anesthesia and for three hours following instrumentation Cocaine hydrochloride 4 per cent is employed The total amount should not exceed 10 cc A cotton pledget is moistened with anesthetic solution and the excess solution is removed Using a curved pharyngeal applicator, the tongue is grasped with dry gauze and the applicator is introduced posterior to the posterior tonsillar pillar Contact is maintained with the lateral wall of the pyriform fossa for one minute This is repeated on the other side Complete anesthesia will be produced after two applications to each fossa

For bronchography another pledget is inserted in the midline over the epiglottis into the larynx between the vocal cords Contact is maintained for one minute Two cubic centimeters of the cocaine hydro

are used beginning with first strength before the patient is considered negative

The indicated strength of P P D is injected intradermally in a dose of 0 1 cc into the flexor surface of the forearm with a 1 cc tuberculin syringe with a 24 gauge needle A small white bleb should be produced Great care should be taken to prevent injecting the tuberculin solution subcutaneously If this occurs no local reaction may be seen and a febrile reaction may result High dilutions of tuberculin lose strength on standing and therefore should be discarded after being used

Interpretation of Results The test should be read forty eight or seventy two hours after the injection Response to injection is classified as positive, negative or *doubtful Positive reactions are rated* + ++ +++ or ++++ depending on the extent of induration measured at its widest diameter A reaction showing some definite induration 5–10 mm in diameter is +, 10–20 mm is ++ and marked redness and induration exceeding 20 mm is +++ A reaction consisting of severe induration and an area of necrosis is ++++ A reaction with slight redness and edema less than 5 mm in diameter is marked doubtful ' If there is no edema at the site of the injection even although a slight redness *is present, the test is* negative The redness is of less significance than the edema Positive reactions mean past or present tuberculous infection *However there is consid*erable discussion at this time regarding the specificity of reaction to high concentrations of P P D, such as the second strength and some have advised discontinuing its use A negative reaction does not invariably exclude tuberculosis as tuberculin sensitivity *may be absent in* acute miliary and terminal tuberculosis, and during some infectious disease Anergy to tuberculin also may develop in Hodgkin s disease and in patients under treatment with ACTH or cortisone

Coccidioidin Skin Test

In coccidioidomycosis sensitivity develops within a few days to three weeks after clinical onset of the disease and persists for at least a year, declining slowly in degree

Coccidioidin in 1 100 dilution is injected intradermally (a tuberculin syringe is used) into the skin of the forearm in a dose of 0 1 cc

Interpretation of Results The test is read at twenty four hours and forty-eight hours Induration of 5 mm in diameter at either time is positive If the 1 100 dilution is negative, the test should be repeated with 1 10 dilution In the low dilutions cross reactions may occur in patients who are histoplasmin positive

The material is nonantigenic and does *not activate the disease or stimulate anti*body formation Patients with proved cavities are almost invariably positive to the test, in contrast to those with the disseminated disease, who are commonly negative to the skin test

Precipitin and complement fixation tests are useful aids in the diagnosis of coccidioidomycosis Precipitins disappear early in the course of the infection In late cases negative complement fixation tests are frequent When positive late in the disease they are often of low titer

Recovery of the organism *from the* sputum or gastric contents of the patient is the most reliable method of diagnosis *Direct smear is of little value and it* is essential to culture the material or inoculate it into animals Lymph node biopsy may reveal *the presence of the organism*

Histoplasmin Skin Test

The specificity of the skin test for histoplasmosis is still somewhat uncertain

A 1 1000 dilution of histoplasmin antigen (0 1 cc) is injected intracutaneously The reaction is noted in forty eight *hours* The results are interpreted as in the tuber

culin test Diagnosis as a result of a positive test in the individual case must be made with reserve

Toxoplasmosis Intradermal Test

This test is most useful for the diagnosis of chronic toxoplasmosis The antigen is obtained from the sediment of mouse peri toneal fluids rich in *Toxoplasma* An injec tion of 0 1 cc of antigen is made intradermally A control antigen is injected in the same amount Reading is made in forty eight to seventy two hours but posi tive reactions usually occur after twenty four hours

Interpretation of Results A positive test is an area of erythema and induration of more than 10 mm diameter This indi cates past or present infection The inten sity of the positive reaction is not correlated with the activity of the disease Dermal hypersensitivity is not acquired early enough for the test to be useful in acute toxoplasmosis

Other tests such as the toxoplasma neu tral zing antibody test and the complement fixation test are less useful

Kveim Reaction

This is an intradermal test for sarcoid osis using antigen prepared either from sarcoid tissue or from normal human spleen

Sarcoid antigen (0 15 cc) is injected in tradermally with an 18 or 20 gauge needle A positive reaction cons sting of a papule may occur in ten days to several months The usual time is six to eight weeks On excision it reveals the characteristic sar coid structure on microscopic examination Recent reports indicate that the Kveim reaction is of definite diagnostic value in sarcoid A positive reaction occurs only in sarcoidosis The antigen however is not readily available

Cold Agglutinins

In primary atypical pneumonia cold ag glutinins appear during the second or third week after the onset of symptoms Maximum titers are found between the middle of the second and middle of the fourth week The titer of cold agglutinins is generally proportional to the severity of the disease

Interpretation of Results A titer of 1 32 or 1 64 in a single convalescent serum is significant A rising titer is especially im portant A fourfold or greater rise in titer in the serum taken in convalescence when compared with that obtained in the early stage of illness is of greater diagnostic importance than is a positive result on a single sample In severe cases of primary atypical pneumonia cold agglutinins are present in over 90 per cent of cases while in mild cases the reaction may be positive in only about 20 per cent

Streptococcus MG Agglutinins

About 50 per cent of patients with pri mary atypical pneumonia develop agglu tinins against *Streptococcus* MG In mild cases agglutinins may develop in only about 20 per cent whereas in severe cases agglutinins develop in over 70 per cent A titer of 1 16 or higher is positive

RADIOLOGIC TECHNICS*

The posteroanterior view of the chest is standard The lateral view is frequently necessary to visualize the interlobar fissures the right middle lobe the paravertebral retrocardiac areas and the mediastinum Oblique views are necessary in broncho graphy and to visualize the lower lobes as lesions from intrapulmonary or parenchy mal involvement Tomograms permit study

* See also Chap er 47

of planes of the lung and are useful in the detection of cavities which may otherwise be obscured Apical lordotic views aid in the delineation of the apices of the lungs by *removing, through* positioning, the ob scuration produced by the clavicles and upper ribs This is done by the patient assuming the lordotic position with the back of the shoulders against the cassette and the abdomen brought forward

FLUOROSCOPY

Fluoroscopy is useful as a screening pro cedure in pulmonary disease Considerable care should be taken not to cause overex posure for either the patient or the physi cian A maximum time of three minutes should not be exceeded for the exposure Thorough accommodation by the physi cian will reduce the time of the exposure and increase the value of the procedure Ten to fifteen minutes in the dark room is required for adequate accommodation The examination should be done in a systematic fashion The size, configuration and movement of the heart are observed The diaphragm and costophrenic sinuses should be examined closely Excursions of the diaphragm are noted Abnormal densi ties within the lung fields are examined with a small aperture of the diaphragmatic shutter Shift of the mediastinum on lateral movement of the patient and on inspira *tion or expiration should be noted*

Miscellaneous Procedures

INTRADERMAL TEST FOR FILARIASIS

A significant number of veterans of World War II have been in zones endemic for filariasis and have acquired the infec tion This procedure supplements direct examination of the blood for filaria

Dirofilaria immitis antigen (0 01 to 0 02 cc of 1 8 000 dilution) is injected intrader mally A control solution of normal dog serum is injected into the *opposite arm* A positive reaction is of the immediate type and appears within fifteen to twenty minutes after injection In rare cases there may be a delayed reaction after twenty four hours The formation of a wheal larger than that of the control by 4 mm or more with or without pseudopodia is a positive reaction The wheal is usually surrounded by a zone of erythema, but the amount of erythema is not as important as the size of the wheal and the presence of pseudo podia

COMPLEMENT-FIXATION TEST FOR FILARIASIS

As an additional check, at least 2 cc of perfectly clear blood serum preserved with 0 02 cc of a 2 per cent aqueous solution of merthiolate per cc of serum, should be sent to the National Institute of Health U S Public Health Service, Bethesda *Maryland* The serum should be obtained from the patient in the fasting state, under sterile conditions

MALARIA

Thin and thick smears should be pre pared and stained with Wright s or Giem sa's stains If the thin smear is negative the thick smear should be examined The thin smear is prepared in the usual fashion The thick smear is prepared by placing a *large drop of* blood on the slide and then spreading it with a needle, using a rotating motion so that the red blood cells are sev

eral layers thick in the center, tapering off to a single layer at the margin The thickest part of the smear should not be opaque It should dry thoroughly over night or in an incubator for one hour at 37° C Thin and thick smears are placed on the same slide

Epinephrine Test

The injection of epinephrine to contract the spleen and increase the parasite density in the peripheral blood is of no value and should be abandoned

Occasionally a positive smear for malaria may be obtained from the bone marrow when the peripheral blood has failed to reveal parasites

SPINAL TAP

A funduscopic examination should precede any lumbar puncture, since the procedure is contraindicated in the presence of increased intracranial pressure as indicated by papilledema

The patient lies in the lateral recumbent position The site usually selected is the interspace between the third and fourth lumbar vertebrae, which is on a line with the iliac crest The skin is prepared with antiseptic solution and infiltrated with 1 per cent procaine The head is flexed on the chest and the knees are drawn up on the abdomen With the patient s back in the exactly vertical position at the edge of the bed the spinal puncture needle is inserted in the midline directed cephalad until a yielding sensation is felt as the dura is pierced The stylet is removed and a water manometer is attached Following determination of the pressure readings 5 cc of spinal fluid is collected in each of two tubes and sent to the laboratory for examination for cell count, protein, Wassermann, colloidal gold sugar chlorides and smear and culture as indicated

Normal values are as follows

Cells	Less than 10 lymphocytes per cmm
Chlorides as NaCl	720–750 mg per 100 cc.
Colloidal gold	Not more than one in any tube
Glucose	45–65 mg per 100 cc
Protein	15–40 mg per 100 cc
Pressure	100–200 mm water

QUECKENSTEDT TEST

With the water manometer attached to the spinal puncture needle, compression is made over each jugular vein separately and together The patient is asked to strain as though moving his bowels He is told to cough and pressure may be exerted by an assistant over the abdomen A reading of the spinal pressure is taken before each procedure The height of the rise of the column in the spinal manometer is noted during each maneuver and the time in seconds is measured for the pressure to return to the initial reading

Interpretation of Results Normally there is a sharp rise in pressure up to 35–50 cm followed by a sharp fall to the initial reading within ten seconds following each maneuver This test is used to determine the presence of subarachnoid block If there is a complete block, there is no rise With partial block there is a slow rise and a slow fall

If the initial pressure is high, 2 to 4 cc of fluid are removed slowly The pressure is then rechecked The pressure should not be reduced more than one half of its height above the normal figure of 200 mm of water

AYALA'S INDEX

This may be useful in differentiating subarachnoid block due to a tumor, from increased pressure due to meningitis hydrocephalus or hypertensive encephalopathy

The initial pressure is recorded, 10 cc of spinal fluid are removed and the final pressure is recorded Ten times the final

pressure divided by the initial pressure yields the index Normal values are 5 5 to 6 5

A reading of under 5 points to a small reservoir as in tumor or some other expanding lesion Over 7 means a large reservoir, as in serous meningitis or hydrocephalus

CISTERNAL PUNCTURE

This procedure is indicated infrequently for the collection of cerebral spinal fluid, or for drainage of the subarachnoid space in the presence of block lower down

The occiput and base of the neck is shaved and an antiseptic applied The skin subcutaneous tissue and muscle are infiltrated with 1 per cent procaine With the patient sitting up the head is held by an assistant flexed on the chest in the center of the body An 18 gauge spinal tap needle is introduced exactly in the midline below the occipital protuberance and above the second cervical spinous process The needle is directed upward toward the glabella on a line with the external auditory meatus It is advanced slowly until the dura is punctured and spinal fluid is encountered This occurs at a distance of 3 to 5 cm Frequent aspiration with the syringe is helpful Spinal fluid is sent to the laboratory for examination, as indicated under spinal tap This procedure is not without danger, and should not be undertaken lightly

ANAMNESTIC REACTION

An increase in antibody titer may occur following the injection of a variety of non specific substances other than the original antigen It is important to remember that during any acute febrile illness a rise in agglutinins for an unrelated disease may occur and confuse the picture This may result because of a previous immunization or illness Thus, the widespread use of immunization procedures against typhoid and cholera in military personnel may subsequently produce agglutinins for these diseases in unrelated febrile illnesses Cross agglutinins as a result of previous immunization for cholera, may appear against tularemia and brucellosis, and thus introduce confusion, unless properly interpreted

CREATININE EXCRETION

Creatinine is almost completely excreted in the urine and has been employed as a test for the primary myopathies Normal values are 8–11 mg per kg body weight in twenty four hours for males and 5–8 mg for females

The excretion of creatinine is reduced in primary myopathies and in renal insufficiency It is increased in wasting diseases due to increased tissue catabolism

NEOSTIGMINE TEST FOR MYASTHENIA GRAVIS

Neostigmine methylsulfate in a dose of 1 5 mg is injected intramuscularly with 0 65 mg of atropine sulfate to prevent gastrointestinal irritability Neostigmine may also be injected intravenously in a dose of 0 5 mg

A positive test is the abolition of the symptoms of the disease in fifteen to thirty minutes after intramuscular administration or in 5 minutes after intravenous injection

In mild cases, quinine sulfate in doses of 0 3–0 6 mg may be given orally This will exacerbate the manifestations of the disease if positive

MILLIEQUIVALENTS

In recent years there has been a considerable trend to the use of 'milliequivalents per liter' (mEq /L) for the measurement of chemical components of the extracellular fluid The value is obtained by dividing mg per liter by the atomic weight and multiplying by the valency By employing terms of chemical equivalents, the relative magni

tudes and interrelations of the different constituents can be better appreciated

MILLIOSMOLS

The osmotic pressure of extracellular fluid is expressed in terms of ionic concentration without regard to valency The value of milliosmols per liter is obtained by dividing mg /L by the atomic weight

EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS

Exfoliative cytologic technics such as the Papanicolaou method represent an important advance in the early diagnosis of cancer The Papanicolaou method involves the special staining of smears of secretions and sediments obtained from various body tissues Diagnosis is based on individual cytologic characteristics and interpretations are graded on a basis of I to V Class I and II are negative Class III is suspicious Class IV and V are positive The method has its greatest applicability as a screening procedure and in situations where biopsy is *not feasible It is most useful in suspected* lesions of the cervix and uterus Examinations of sputa and bronchial secretions for cancer of the lung have been found to be of value by individuals with extensive experience in cytologic diagnosis In one study, the over all percentage of accuracy was 55 When a series of 5 sputum specimens was examined the sensitivity rose to 90 per cent in 130 proven cases In gastric carcinoma the upper limit of accuracy of the method under optimum conditions is 60 per cent False positives occur in most reported studies

The procedure has also been applied with indifferent success to the examination of the urinary sediment for the diagnosis of cancer of the urinary tract, to prostatic secretions, the colon, and serous fluids

Diagnosis by exfoliative cytologic methods has significant limitations These are due to factors inherent in a method based on examination of individual cells rather than on sections of tissue Certain tumors such as scirrhous carcinomas do not exfoliate adequately Localization by cytologic study in cancer of the urinary tract is poor Considerable time and extensive training in interpretation are mandatory

A modification employing sponge biopsy with a gelfoam swab according to the technic of Gladstone, has been applied to the diagnosis of cancer in accessible regions of the body The sponge is rubbed over the suspicious area, sectioned in the usual fashion and examined Since this method depends on accessibility it has few advantages and considerable limitations in comparison to conventional biopsy

50. Toxicologic Problems

W. J. R. CAMP

WHILE many of the statements in this chapter may seem trite they have been included because experience has dictated them Perhaps because of the paucity in the teaching of toxicology in the medical curriculum and because of the comparative infrequence of poisoning cases physicians seem to consider them as separate from general medicine However the utter abandon with which new drugs compounds and preparations are put on the market and the extreme rapidity of industrial expansion merely adds to the frequency with which poisons are taken or produce morbidity The treatment of these morbidities does not differ basically from the treatment of intoxications due to other causes While it is true that some poisonings are acute and fulminant, and require immediate treatment, it is equally true that many are subacute or chronic. Chronic arsenic and lead intoxications still rank high in frequency among poisoning cases

Source of Poisons

WHILE there is a sharp demarcation between industrial and nonindustrial poisoning as far as the source of toxic material is concerned there is a great overlapping in place of treatment Often a person who has been exposed to a toxic substance prefers to go to the family doctor rather than to a company physician The patient may no longer work where the exposure had taken place and may even forget that he had been exposed Not uncommonly a general practitioner is called in to treat industrial intoxications occurring in small plants which do not have the benefit of a plant physician While this overlapping is recognized, the material in this chapter is directed to the general practitioner Industrial intoxications will be considered only to a minor degree

It is paramount that in any case where chronic poisoning is suspected a very complete occupational history for a period of years be developed It is not safe to assume that a man complaining of abdominal cramps who says he is a painter is suffering from lead intoxication It is necessary to know how long he has been a painter what kind of painting he does and what kind of paint he uses Many paints contain no lead Peripheral neuritis is not always due to

lead or arsenic, although experience leads one to believe many physicians think so Strangely, alcohol is not too commonly con sidered as an etiologic factor One never wastes time by developing a very complete occupational and personal history of a pa tient suspected of having some chronic in toxication—or as a matter of fact of any patient

DOMESTIC POISONS

Poisons are taken or administered by in tent, through accident through innocent exposure, through industrial exposure or by overdosage in treatment It is obvious that none of these could occur if proper precautions were taken

Accidental ingestion of poisons by chil dren could be eliminated were parents alert to keep such substances out of reach The average home is a storehouse of poisons and children cannot be expected to differentiate toxic from harmless mate rials when the parents refuse to do so

Through lack of information or disre gard for safety toxic materials are often stored in juxtaposition to edibles A can of sodium fluoride is stored next to one of flour, and used by mistake to prepare pan cakes Mercuric bichloride tablets are put into an old aspirin bottle and set next to a bottle containing aspirin The child who drinks coal oil laundry bleach, 'lysol ' or perfume from a bottle is attempting to satisfy thirst If the youngster takes pills from the medicine cabinet it is because mother or father did it, and any dire con sequences actually should be attributed to parental neglect in not keeping such mate rial safely stored away It is part of a physician s duty to inform his patients of such possibilities

Physicians could help by not prescribing large amounts of toxic substances Too often incompletely used bottles of medicine or boxes of pills are not destroyed The *labels may then be lost and regardless of* what the original dose may have been, a teaspoonful is considered by the average user as a fair dosage at a later time often with serious results Judging from toxi cologic experience barbiturates almost al ways are prescribed in excess of the demon strated need This unquestionably accounts for many of the accidents which occur with this group of drugs *

* See also Chapter 4

General Treatment

BASICALLY the general treatment of a pa tient who is suffering from poisoning is the general treatment that should be extended to any patient

The condition of the patient must be con sidered serious or potentially serious until recovery is complete Such patients should be at rest and should not be exhausted by overtreatment Since shock is apt to occur in many cases treatment should be directed toward preventing or correcting it The treatment of shock due to poisons does not differ from treatment of shock due to other causes * In view of the fact that commonly one must rely on symptomatic treatment the patient should be watched closely and cor rective measures originated as soon as pos sible

In addition one must be on the alert for etiologic factors other than the poison which may induce similar symptoms, or which may exist concomitantly without specific symptomatology A person who has

* See also Chapter 39

been drinking is not necessarily comatose because of the alcohol A skull fracture or injury to an internal organ may be present That a combination of poisons may be acting must be kept in mind Common combinations encountered are alcohol and barbiturates and heroin or morphine and barbiturates in addicts Acute alcoholics too frequently have their stomachs washed out and then are discharged without further examination It cannot be emphasized too strongly that a particular odor on the breath or about the patient does not mean necessarily that the condition of the patient is due to the odoriferous substance

A patient should not be discharged completely from medical observation because he is asymptomatic An individual who has used paint remover in a closed room for several hours may in a short time feel normal but nevertheless he should have blood counts done for some time afterwards until aplastic anemia is no longer a possibility Similarly a person who has been exposed acutely to a halogenated hydrocarbon (as in degreasing processes) should be checked at intervals to be sure no liver damage has occurred

Awareness of the complications and sequelae of poisoning is mandatory The pneumonia following barbiturate intoxication and the amnesia occurring after exposure to carbon monoxide are examples of such sequelae A patient who has recovered from a barbiturate induced coma should not be discharged without assurance that the lungs are clear

SEPARATION OF PATIENT AND POISON

It is clear that the patient and the poison must be separated This is simply done when a gaseous poison such as carbon monoxide methyl chloride or ammonia is involved The victim is removed to an area where fresh air is available proper treatment is instituted including the use of artificial respiration or pulmotor,* and the patient transported to a hospital for continued adequate treatment While first aid is being administered the patient should be kept warm If recovery takes place before hospitalization the victim should not be permitted to get up and walk about Sudden circulatory collapse may endanger life The patient should be kept prone warm and quiet In any event it is safest to hospitalize such patients for a minimum of forty eight hours to make sure no complications develop and that any required treatment can be instituted immediately

Lavage

Since poisons are commonly taken by mouth, removal of the noxious substance from the stomach should be done immediately Often the nature of the poison is not known and gastric washings taken before administration of an antidote may be *the only means of identifying the poison* and hence of establishing subsequent rational therapy

Copious quantities of water or isotonic solution of sodium chloride in small but measurable amounts probably serve best Large quantities should not be used at one time since there is danger of forcing the material into the duodenum where absorption may occur It is imperative that the quantity given must be aspirated Material withdrawn should be discarded and fresh wash used each time The wash should not be injected under pressure Every care must be taken to insure a to and fro movement from the stomach only One should not assume that lavage has done more than remove a fair portion of the material ingested Subsequent therapy must be pursued as intensively as if lavage had not been done

Specific solvents for known poisons must be used with extreme care since a substance in solution may be more readily absorbed Whenever a specific solvent—such as di

* See al o Chapter 44

luted alcohol in phenol intoxication—is used, one must be extremely careful to remove all the wash from the stomach

While it is common practice to administer universal or specific antidote through the stomach tube after lavage, too much reliance should not be placed on this procedure It is true that inactive compounds may be formed in the stomach but it is equally true that such compounds may be reactivated lower in the gastrointestinal tract Hence it is imperative that the stomach again be washed free of the antidote There is little to be gained in administering tannic acid in a case of strychnine poisoning if the strychnine tannate is not removed and therefore subsequently hydrolyzes in the intestines If it is felt after repeated administration and aspiration of the antidote that practically all of the poison has been removed a residual amount of antidote may be left in the stomach since small amounts of poison are hydrolysed slowly enough so that toxic levels are not reached

It is well to remember that the stomach is not a test tube, and that it is not possible to neutralize a strong acid with a strong alkali Dilute solutions must be used By using large quantities the poison is not only diluted but also is gradually neutralized When a corrosive acid has been ingested alkaline materials which liberate carbon dioxide should not be used because of danger of distention and rupture of the stomach Similarly when lye has been taken, treatment should be with diluted vinegar, or acetic acid lemon juice etc Oxidizing solutions such as potassium permanganate must be dilute 1 5000 or 1 10 000 and should not be permitted to remain in the stomach

Whether a stomach tube should be passed or not must depend on clinical judgment Certainly there are cases (lye, strong acids corrosives) in which such manipulation could be dangerous On the other hand, the procedure may be life saving

EMETICS

While the use of emetics is commonly advocated their effectiveness often is dubious With the exception of apomorphine emetics act by initiating a reflex in the stomach wall If the stomach wall is irritated by the poison, vomiting will occur and an emetic is not needed This is the common reaction to "lysol," the soap acting as the emetic Such a patient should be given repeated copious draughts of water to aid in washing the stomach If the stomach mucosa is corroded or otherwise altered or if the vomiting center is depressed by a poison vomiting may not occur after use of mustard or zinc or copper sulfate

In addition, vomiting permits the poison to act a second time on the mucosa of the esophagus and mouth and inhalation of vomitus is always a possibility When one considers the discomfort to the patient, and the possibility of rupture of the stomach when corrosive materials have been taken, gastric lavage seems a much saner and more effective procedure than use of emetics

It is obvious that emetics should never be administered to an unconscious patient

While apomorphine may effect emesis when a peripherally acting emetic is ineffective, it should not be used if the patient is depressed, since it may aggravate the depression without inducing vomiting

ANOXIA*

In general, substances which may depress the respiratory mechanism such as barbiturates, opium derivatives, alcohol, and some anesthetic agents may produce anoxic anoxia Anemic anoxia is effected by carbon monoxide, by substances producing methemoglobin such as nitrites, nitrates, aniline, and its derivatives by chlorates, and by sul

* See also Chapter 41

fonamides and substances producing sulf hemoglobin (sulfides)

In anoxic anoxia the treatment must be directed to increasing available oxygen This is best done with inhalation of high concentration of oxygen with or without carbon dioxide as the patient requires Carbogen is definitely indicated in carbon *monoxide poisoning If the hemoglobin has* been altered so that it cannot carry adequate oxygen, venesection followed by whole blood (not plasma) is indicated

The use of respiratory stimulants without the use of oxygen is questionable since the respiratory center is depressed and the *stimulants increase the center s demand for* oxygen Further, the stimulants are not necessarily specifically antagonistic to the substance causing the depression

A patient may tolerate an astounding degree of methemoglobinemia providing it has developed over a long enough period such as results following routine taking of headache powders containing acetanilid This form of chronic methemoglobinemia does not require the emergency treatment necessary when methemoglobinemia develops quickly

In the treatment of cyanide intoxication with nitrites one should not permit a *severe degree of methemoglobinemia to* develop for this would merely be the substituting of one type of anoxia for another

STIMULANTS

Poisons more frequently cause depression than stimulation Since many of the more common substances taken in overdosages—alcohol barbiturates, opium derivatives and synthetic subs*titutes—tend to create* an anesthetic state treatment should be that of anesthetic overdosage primarily the administration of oxygen and general cardiovascular support Oxygen is more efficacious and less liable to effect untoward reactions than are the respiratory stimulants which increase the demand for oxygen

Stimulants Commonly Used

Picrotoxin (barbiturate intoxication), 1 mg per minute intravenously until the corneal reflex returns (overdosage should be avoided)

Caffeine sodium benzoate, 0 5 Gm given intramuscularly Smaller doses are not of much value

Ephedrine sulfate, 25 mg given intramuscularly or subcutaneously If used too *frequently, the patient may become restless* It should not be used if the patient has high blood pressure and possibility of a vascular accident exists

Amphetamine sulfate, 30 mg every thirty *minutes given intravenously The same care* should be employed as noted under ephedrine sulfate

Metrazol, 100 mg administered intramuscularly or intravenously The dose may be repeated as needed

Strychnine sulfate, 1 mg given subcutaneously This may be repeated up to a total dose of 6 mg It is not too effective since its main action is on the spinal cord

Nikethamide, 1 to 3 cc of a 25 per cent solution may be given intravenously It should be used with care since it can induce convulsions and respiratory arrest

DEPRESSANTS*

Short acting barbiturates as *pentobarbital sodium* or *amytal sodium* (0 1–0 3 Gm intravenously) are most effective in the treatment of hyperexcitable states or convulsions, but should not be given in such quantities that the patient is depressed Long acting barbiturates should not be used It is safer to just control the hyperexcitability and repeat the dose of antidote than to give large doses which may become depressing

Morphine or codeine should not be used when hyperexcitability is present

* *See also Chapter 22*

Paraldehyde may be given rectally in 4 to 8 cc doses but is not too effective if motor activity is marked

Chloral hydrate should not be used since the amount necessary to effect motor depression is too close to the toxic dose

ANTIDOTES

Universal Antidote

The so called universal antidote consists of activated charcoal 2 parts with 1 part each of magnesium oxide and tannic acid The carbon must be activated since ordinary charcoal has little adsorbing power It should be used in liberal doses—5 Gm, repeated frequently It should not be permitted to remain in the stomach Magnesium oxide is a mild alkali and useful to neutralize acidic poisons The tannic acid precipitates alkaloids, metals and some glucosides but the resulting compounds must be removed since on hydrolysis the original poison is released The universal antidote is suspended in water and administered through a stomach tube The material is then withdrawn and fresh antidote given In no case should treatment be solely confined to administration of this antidote

Demulcents

Demulcents such as barley water egg white, milk, starch water, and oatmeal gruel are commonly used when irritative poisons have been taken While these may be effective to some degree if the irritant is mild, it is difficult to believe they are of much value if a corrosive irritant is present In toxicologic experience, stomachs which have been exposed to nitric, sulfuric or hydrochloric acids lye ammonium hydroxide corrosive chloride of mercury, phenol fluorides, etc, invariably have damage to the total mucosa Demulcents then could do no more than create a protective coating against further action of the corrosive, but irreparable damage is usually complete before the demulcent can be given

Specific Antidotes

Whenever possible specific antidotes should be administered The difficulty is that often the identity of the poison is not known (Specific antidotes will be given under the consideration of each poison)

Physiologic Antidotes

Physiologic antidotes are used to effect a state in most cases opposite to that produced by the poison, such as ether or barbiturates to control convulsions, or atropine to inhibit the effects of overdosage of neostigmine and similarly acting drugs The dosage of such antidotes is the amount just sufficient to control the adverse symptoms Under no circumstances should toxic phenomena be superimposed by the antidote It is rather disheartening to see picrotoxin often given to the point where its toxic symptoms have to be controlled by a barbiturate when barbiturate intoxication was the original reason for picrotoxin administration

Dimercaprol (BAL)

British Anti Lewisite is effective in the treatment of intoxications due to arsenic (relatively common) gold (relatively uncommon since it is due to overdosage in treatment) and mercury (less common than arsenic) It is not too highly effective in the treatment of bismuth and antimony poisoning It may increase the toxicity of lead cadmium, and selenium

Dimercaprol is marketed in ampuls containing 10 per cent dimercaprol in peanut oil and 20 per cent benzyl benzoate It is to be injected intramuscularly *Never give it intravenously*

Dimercaprol is administered in doses of 3 mg per Kg body weight In less severe

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Demulcents such as barley water, egg white, milk, starch water, and oatmeal gruel are commonly used when irritative poisons have been taken While these may be effective to some degree if the irritant is mild, it is difficult to believe they are of much value if a corrosive irritant is present In toxicologic experience, stomachs which have been exposed to nitric, sulfuric or hydrochloric acids lye ammonium hydroxide corrosive chloride of mercury, phenol fluorides, etc, invariably have damage to the total mucosa Demulcents then could do no more than create a protective coating against further action of the corrosive, but irreparable damage is usually complete before the demulcent can be given

Specific Antidotes

Whenever possible specific antidotes should be administered The difficulty is that often the identity of the poison is not known (Specific antidotes will be given under the consideration of each poison)

Physiologic Antidotes

Physiologic antidotes are used to effect a state in most cases opposite to that produced by the poison, such as ether or barbiturates to control convulsions, or atropine to inhibit the effects of overdosage of neostigmine and similarly acting drugs The dosage of such antidotes is the amount just sufficient to control the adverse symptoms Under no circumstances should toxic phenomena be superimposed by the antidote It is rather disheartening to see picrotoxin often given to the point where its toxic symptoms have to be controlled by a barbiturate when barbiturate intoxication was the original reason for picrotoxin administration

Dimercaprol (BAL)

British Anti Lewisite is effective in the treatment of intoxications due to arsenic (relatively common), gold (relatively uncommon since it is due to overdosage in treatment), and mercury (less common than arsenic) It is not too highly effective in the treatment of bismuth and antimony poisoning It may increase the toxicity of lead cadmium, and selenium

Dimercaprol is marketed in ampuls containing 10 per cent dimercaprol in peanut oil and 20 per cent benzyl benzoate It is to be injected intramuscularly *Never give it intravenously*

Dimercaprol is administered in doses of 3 mg per kg body weight In less severe

cases, 2 5 mg per kg will suffice A simple formula for the dosage is

$$\frac{\text{Weight in pounds}}{75} = \text{Cubic centimeters BAL (approx)}$$

It should be given every four fours for forty eight hours, then four times on the third day and twice a day thereafter for ten days or until recovery

Dimercaprol may induce pain at site of injection nausea vomiting headache burning sensation of lips throat, and eyes salivation sweating of forehead and hands lacrimation, tingling muscular aches sense of constriction in the chest tachycardia fever agitation The symptoms usually begin within fifteen minutes reach a climax shortly and subside within two hours

Toxic Doses

THE designation of toxic doses of any material is of little value nor is the statement that patients have recovered from such and such a dose beneficial since it may lead to false consideration of the case at hand Every patient who is suffering from toxic effects of a substance must be treated as though a lethal dose had been ingested Recently a student read in a textbook that recovery had occurred after a person had taken 29 Gm of chloral hydrate He took this amount of the drug apparently in an attempt to verify the statement He was unsuccessful The printing of minimum lethal' and maximum recovery doses seems to be wholly unreliable

If a patient fails to wake up after taking 0 2 Gm of a barbiturate, the only conclusion which may be reached is that 0 2 Gm was lethal for that patient It does not establish *that amount as either the minimum* lethal dose or even the toxic dose for anyone else It has absolutely no significance *as far as other persons are concerned*

On the other hand, the establishment of maximum concentrations of toxic material in the air is highly important industrially These figures are set below any concentration which will produce toxic *effects in the* vast majority of workers but no one should interpret them as being entirely safe for all workers *There is* always a deviation from the normal

Treatment of Individual Poisonings

WHILE it is recognized that the following list of poisons is limited, *it is compiled* from those substances most commonly encountered in the Chicago area It is futile to consider all substances which may cause toxic symptoms since the number is legion With the ready *availability of so many* poisons it is a wonder that more morbidities or mortalities do not occur

By necessity the greater part of treatment must be symptomatic since specific antidotes are lacking Specific detoxications which may occur in a test tube do not necessarily occur in the body While potassium permanganate may be used to titrate oxalic acid in the laboratory, it is evident that these substances cannot be used as mutual antidotes since both are toxic and the *reaction which occurs* in glassware is conspicuous by its absence in the body

CARBON MONOXIDE

Common in winter time Remove the patient from the source of gas Keep the patient warm and prone Use artificial respiration or pulmotor to maintain respiration Administer carbon dioxide 6 per cent and oxygen 94 per cent Keep the patient in bed for a minimum of twenty four hours Do not permit the patient to get up too early as there is danger of circulatory collapse Coma which continues after all carbon monoxide has been excreted may be treated with procaine hydrochloride 50 mg intravenously but results are not constant

BARBITURATE

Common Treatment will vary with the condition of the patient If seen soon after ingestion gastric lavage should be performed If depression is not marked mild stimulation (caffeine sodium benzoate) may be used If anoxia or marked depression is present oxygen inhalation is imperative* An airway should be used since there is a tendency for mucus to collect Pulmonary edema and bronchopneumonia are common The patient must be watched carefully and antibiotics given either prophylactically or as soon as indicated The use of stimulants or analeptics is open to question From clinical experience it would seem that those cases of barbiturate intoxication which recover after use of stimulants would recover without any such medication Since barbiturates are distributed to all parts of the brain equally a combination of stimulants would seem to be more logical than merely picrotoxin or any other one alone

General supportive measures should be instituted and the patient kept hospitalized for forty-eight hours after consciousness returns Periodic examination of the chest should be done during this time

It should be noted that death may occur within twenty to thirty minutes after taking a quantity of barbiturate, hence treatment should be instituted promptly Examination of the stomachs of a number of fatal cases shows a marked acute gastritis probably due to the high alkalinity of the sodium barbiturate compounds Depression from large doses of long acting barbiturates may last as long as a week Pneumonia invariably develops in these cases

All barbiturates when taken in overdosage usually appear in the urine, the possible exception is pentothal

Diuretics do not seem to hasten elimination of barbiturates fluid balance must be maintained Emetics are of no value because they enhance the marked depression If the patient is seen several hours after taking the barbiturate absorption is probably already complete, but lavage should be carried out

ALKALOIDS

Strychnine

Not common Found in rat poison Medicinal preparations containing strychnine often cause poisoning in children Do not attempt to wash out the stomach until the patient has been depressed with a short acting barbiturate given rectally or intravenously* If the paroxysms are severe carefully control them with ether, do not use chloroform When the patient is quiet cautiously pass a stomach tube as there is danger of stimulating convulsions Wash out the stomach with an alkaline wash Then administer activated charcoal but be sure it is removed Tannic acid may be used or strong infusion of tea This too must be removed Keep the patient quiet and away from sharp noises sudden bright lights or any other sensory stimulation Repeat the short acting barbiturates when necessary Morphine is contraindicated Do not use long acting barbiturates (bar

* See Chapter 44

* See Chapter 22

bital phenobarbital) Do not disturb the patient any more than is necessary to just control convulsions Maintain respiration with oxygen

Morphine and Related Substances

Overdosage of heroin in addicts is the most commonly encountered condition Poisoning due to oral ingestion is rare Do not allow the patient to lapse into semi coma or sleep Everything possible should be done to keep patient awake and active The patient should be kept warm Stimulants may be helpful Atropine is danger ous since if the dose is not correct it may increase the morphine depression Amphet amine or ephedrine is preferred

If coma has supervened, oxygen with or without carbon dioxide should be used It is of prime importance to keep the respir atory center reactive Addicts commonly take barbiturates to supplement or com plement a dwindling supply of heroin and since the barbiturate is taken intrave nously death not uncommonly occurs The addict also uses barbiturate to obtain sleep particularly when on restricted amounts of opiate One addict obtained three hours sleep after taking 1 2 Gm of pentobarbital orally

Nalline seems effective against the natural alkaloids or synthetic substitutes

ARSENIC

Most common source of acute metal poisoning Most commonly arsenic is taken as arsenic trioxide or an arsenite Copious gastric lavage is required as arsenic trioxide *is not easily soluble* Administer dimercap rol (BAL) immediately Saline catharsis is valuable to rid the gastrointestinal tract of arsenic Maintain kidney function to aid *excretion* Collapse is common if much arsenic has been taken The patient must be recumbent Cardiovascular collapse may occur Symptomatic treatment should be administered as needed Absorbed arsenic is slowly excreted abnormal amounts have been found in the hair two years after the last therapeutic dose of carbarsone

Chronic arsenic intoxication has no fixed symptomatology It may imitate many clin ical conditions and its diagnosis can only be suggested after chemical studies of hair and urine Dimercaprol is effective

LEAD

Most frequent of metal poisonings usually subacute or chronic The most effi cient antidote in controlling symptoms and inactivating lead is disodium phosphate Four grams are given as a single dose, re peating three times a day or every few hours depending on the severity of the condition Twenty cubic centimeters of a sterile 1 per cent solution may be given intravenously slowly

Sodium citrate in 5 Gm doses may be given orally, or 50 cc of a 25 per cent solu tion may be given intravenously

Cathartics are not necessary when phos phate is given orally De-leading of a pa tient should not be a prime consideration When done it should be very gradual and performed over a long period of time Drawing out too much stored lead may induce an acute exacerbation Mobiliza tion of lead will occur during acidosis or alkalosis A diet adequate in calcium and vitamin D should be maintained

MERCURY

Not very common Administer egg whites or milk and wash out stomach Repeat several times Be sure the mercury protein complex is removed by lavage Do not permit it to remain in the stomach since mercury will be liberated subsequently Lavage with a 5 per cent solution of so dium formaldehyde sulfoxalate may be used Dimercaprol should be given immed iately Kidney function must be watched carefully since the kidneys are the prime point of attack of mercury If nephrosis is

present fluids must be limited until tubular regeneration has occurred With complete anuria 750 cc of fluid daily will balance amount lost by evaporation and expiration Excessive fluids should not be given Diuretics are contraindicated

OTHER METAL POISONINGS

Poisoning from other metals is not common outside of industry No specific antidotes are available for such poisons as cadmium or thallium While dimercaprol may be employed it should be used with extreme care since symptoms may be aggravated by the antidote

FLUORIDES

Treatment should be directed to inactivation of fluorides with calcium Lavage with lime water or chalk suspended in water Calcium gluconate 1 Gm should be administered intravenously to increase the available calcium Milk can be used it acts both as a demulcent and as a fluoride inactivator Keep the patient warm and recumbent Otherwise symptomatic treatment is indicated

VOLATILE HALOGENATED HYDROCARBONS

Compounds such as carbon tetrachloride chloroform or ethylene dichloride produce danger of liver and kidney damage Intoxication is usually the result of inhalation Respiration should be maintained A high carbohydrate high protein low fat diet should be supplemented by glucose and methionine given intravenously Alcohol is contraindicated Treat the patient as though a toxic hepatitis and nephrosis existed

PHOSPHORUS

Not common Yellow phosphorus is the toxic form of the element Perform gastric lavage with a 1–2 per cent copper sulfate solution Continue lavage as long as any black globules are found in the wash A subsequent wash with dilute potassium permanganate may be used to oxidize the phosphorus but more reliance should be put in the copper sulfate Avoid the use of fats and oils with the exception of liquid petrolatum because phosphorus is soluble in oils and absorption is thereby increased Liver damage may be marked Glycine and glucose may be given for their protective value Other treatment is symptomatic.

PETROLEUM PRODUCTS

There is no specific antidote for poisonings from kerosene, gasoline, naphtha and benzine Kerosene intoxication is comparatively common in children Aspiration pneumonia is not uncommon Gastric lavage should be instituted with 5 per cent sodium bicarbonate Sixty cc of liquid petrolatum may be left in the stomach otherwise treatment is symptomatic If toxic symptoms follow inhalation, remove the patient to fresh air but keep warm and recumbent

Again there is no specific antidote for benzene toluene or xylene Lavage the stomach if taken by mouth remove to fresh air if inhaled Maintain respiration Danger of aplastic anemia exists therefore follow the blood picture for a considerable time after recovery

CYANIDES

Not common Treatment must be instituted immediately The cause of death is a cellular (histotoxic) anoxia. Although the blood oxygen content is high the cells can not use it Basic treatment is directed to converting hemoglobin to methemoglobin which inactivates cyanide Care must be taken not to develop too high a methemoglobinemia since the resultant anemic anoxia is also dangerous Amyl nitrite 0 3 cc by inhalation may be used for half a minute and repeated every few minutes however, extremely low blood pressure

should not be allowed to persist Simultaneously give 0 3 Gm of sodium nitrite (must be fresh) in 10 cc of water intravenously A minimum of two minutes should be allowed for this injection *Follow this immediately through the same* needle with 50 cc of 25 per cent sodium thiosulfate solution Repeat the entire treatment in a half hour with half doses If the victim is alive at the end of half an hour the chances of recovery are very good but the patient must remain recumbent *Subsequent treatment is symptomatic*

If an alkaline cyanide (sodium or potassium) has been taken gastric lavage is indicated but care must be used in passing the tube to avoid perforation A severe gastritis due to the high alkalinity is present but do not use acid wash since this would further irritate the mucosa

Methylene blue is a rather disappointing antidote for cyanide

ALCOHOLS

Acute ethyl alcoholism is the most common form of poisoning Gastric lavage is the preferred treatment emetics should not be used Apomorphine may increase depression Oxygen with or without carbon dioxide *should be used as needed* The blood alcohol concentration should be determined one can anticipate recovery if it is less than 0 3 Gm per 100 cc Keep the patient warm and supply fluids

The administration of *paraldehyde is* like giving more alcohol The barbiturates are dangerous even to control restlessness since they effect a synergistic toxic action with alcohol Maintain respiration and kidney function for excretion of alcohol Stimulants or activity do not increase the rate of metabolism of alcohol If the drinking bout has lasted for several days the liver has become fatty but unless the condition is an acute episode of chronic alcoholism vitamin therapy is not a necessity Pneumonia is likely to develop A saline *cathartic preferably* magnesium sulfate 30 to 60 Gm in 120 cc of water, may be given after washing out the stomach Central edema may be combated with 50 per cent glucose intravenously, given slowly as there is danger of pulmonary edema developing if given too rapidly Do not use antabuse *(tetraethylthiuram disulfide) in acute cases* it is not an antidote

Methyl Alcohol

Not common The treatment is similar to *ethyl alcohol poisoning* but it is necessary to combat acidosis with sodium bicarbonate 5 per cent intravenously or 1/6 molar sodium lactate 5 cc per kg body weight This is the most important therapeutic procedure in treatment of wood alcohol intoxication There is no specific treatment for the amaurosis which may develop nor is there any way to predict whether blindness will ensue Treatment otherwise must be symptomatic.

Isopropyl (Rubbing) Alcohol

Not common Treat as methyl alcohol intoxication

BORIC ACID AND BORATES

These are mentioned not because of any specific treatment nor because poisoning is common but because intoxication would not occur if boric acid or borates were not found in nurseries and if mothers were in*structed not to use it for diaper rashes* etc It seems difficult to convince the medical profession that there is no legitimate use for boric acid Most cases occur in nurseries where boric acid solution or borates are *mistakenly used in preparing formulas.* Recently several infant deaths resulted from the erroneous use of a detergent containing 10 per cent borax in preparing formulas Truly a human error but one which could *not have occurred were boron-containing* solutions and powders prohibited in the nursery

The treatment, other than gastric lavage, is purely symptomatic and not highly satisfactory

PHENOL AND RELATED SUBSTANCES

Not common These substances are corrosive 'Lysol' usually induces vomiting because of the soap present Gastric lavage with copious quantities of water probably is the most efficient and safest treatment Alcohol may increase absorption of these substances Oils if used must be removed If the patient complains of severe abdominal pain, the stomach tube must be passed with extreme caution Only clinical judgment can determine whether the dangers of perforation outweigh the beneficial effects Egg white, milk, and protein material should be given since phenols form complexes with protein, but they should not be allowed to remain in the stomach Sodium sulfate can be used for its cathartic action Fluid balance should be maintained and saline solutions given to maintain kidney function Severe irritation of the kidney may result in anuria Otherwise treatment is symptomatic

Phenol can be removed from the skin by flushing with 50 per cent alcohol Phenol is absorbed from the skin particularly from denuded areas and can effect systemic poisoning

IODINE AND IODINE CONTAINING SOLUTIONS

Not common While iodine is very irritating and will effect irritation of mucous membranes and gastritis, it does not commonly cause death Copious lavage with starch water, barley water, rice water or other starch containing materials should be carried out until the blue color indicating the presence of free iodine has practically disappeared Sodium thiosulfate, 25 Gm to a liter of water, may be used for lavage, which should be alternated with the starch water until the return solution is colorless If gastroenteritis develops, it should be treated as outlined in Chapter 17 on gastrointestinal diseases Morphine may be used for pain Treatment otherwise is symptomatic

ACIDS AND ALKALIS

Not common Usually if concentrated acids or alkalis are taken, corrosion and pain quickly induce shock and death The danger of perforation on passing a stomach tube must be weighed Weak alkalis which do not form gases are used for treatment of acid ingestion Magnesium oxide or lime water are probably the most helpful Do not use calcium carbonate, sodium carbonate, or sodium bicarbonate Aluminum hydroxide jel or other acid adsorbing materials may be used with benefit Corrosion of the gastric mucosa may be complete

Of the alkalis lye is most frequently taken household ammonia less commonly than lye Treatment is based on neutralization with dilute acid 1–2 per cent acetic acid or vinegar diluted with an equal volume of water A liter of such solution can only neutralize slightly more than a gram of either the lye or ammonia, hence a lavage if done, must be copious Oils or butter may be given to protect the mucosa, but from the stomachs seen at autopsy it is doubtful that any treatment retards the destruction of the gastric lining Illustrative is the case of a woman who drank a glass of household ammonia and was treated immediately with vinegar and olive oil and taken to a hospital for further treatment Death occurred on the third day The mucosa was practically nonexistent and the fundus of the stomach was still alkaline in reaction It should be noted that solution of strong acids or alkalis in the stomach is accompanied by development of much heat which may have a deleterious action on the mucosa

Treatment for acid or alkali ingestion for the most part must be symptomatic and directed toward preventing collapse and shock. Recovery may be attended by loss of gastric function or esophageal stricture, both of which must be treated as the case dictates.

Oxalic Acid

Not common. Oxalic acid is a corrosive substance which should be treated by administration of magnesium oxide, lime water, magnesium sulfate, or dilute calcium chloride solution, all of which tend to form an insoluble oxalate. Do not use sodium bicarbonate, etc., since soluble oxalates which are toxic are formed. Twenty-five cubic centimeters of a 10 per cent solution of calcium gluconate or of 5 per cent solution of calcium chloride may be given intravenously. Kidney function must be maintained. Blockage of tubules with calcium oxalate crystals is a possibility.

51. Poisoning by Pesticides

BERNARD E. CONLEY

A WIDE variety of naturally occurring and synthetically produced substances are used for pest control in agriculture in industry, and in and around the home These materials are collectively known as pesticides or economic poisons They include such diverse substances as those used to kill insects (insecticides) destroy rodents (rodenticides), control weeds (herbicides) prevent and modify plant diseases (fungicides) fumigants, and repellents

Pesticides or more precisely pesticidal chemicals, are used alone and in combination with other substances The secondary ingredients or additives endow the mixture or formulation with certain properties such as adhesiveness and penetrability and facilitate the application and increase the effectiveness of the finished preparation Since the secondary ingredients frequently alter pesticidal activity and influence the toxicity of the formulation the treatment of poisoning from pesticides must take into consideration the injurious characteristics of the formulation as well as the toxic properties of the constituent pesticidal chemical A list of the principal pesticides, their chemical designations, comparative toxicities, dangerous oral doses and antidotes is presented in Table 65

Insecticides

INSECTICIDES constitute one of the largest and most useful groups of substances used in pest control For arrangement purposes, classification according to chemical structures is preferable rather than on the basis of methods of application (e g as aerosols dusts, gases or sprays) or functional relationships (e g , contact poison stomach poison or fumigant) From a chemical point of view, therefore, insecticides may be subdivided into three major groups—inorganic insecticides synthetic organic insecticides and botanical insecticides (plant products and their derivatives)

INORGANIC INSECTICIDES

Most of the inorganic insecticides are comparatively simple compounds which are usually universally toxic to all forms of life, including man The elements which form compounds sufficiently effective to receive significant use as insecticides include arsenic antimony, boron fluorine, mercury, selenium and sulfur, with ar-

ACUTE TOXICITY OF SOME REPRESENTATIVE PESTICIDES

Preparation: Common name	Preparation: Chemical name	Comparative toxicity*	Dangerous oral dose** (Gm 62 Kg)	Antidotes
		INSECTICIDES		
Paris green	Copper acetoarsenite	Highly toxic	0 1†	BAL
Arsenic trioxide		Highly toxic	0 1†	BAL
Sodium fluoride		Highly toxic	1 0†	—
Sodium fluosilicate	Sodium silicofluoride	Highly toxic	2 5†	—
Cryolite	Sodium aluminum fluoride	Slightly toxic		—
Sodium selenate		Highly toxic	0 2	Bromobenzene
Tartar emetic	Antimony potassium tartrate	Highly toxic	0 15†	BAL
Corrosive sublimate	Mercuric chloride	Extremely toxic	0 07†	BAL
Borax	Sodium borate	Moderately toxic	7 5†	—
DDT	1,1,1-Trichloro 2,2 bis (*p* chlorophenyl) ethane	Moderately toxic	30†	Phenobarbital
DDD	1,1 Dichloro 2,2-bis-(*p*-chlorophenyl)ethane	Slightly toxic		—
Methoxychlor	1,1,1 Trichloro-2,2-bis-(*p*-methoxyphenyl) ethane	Practically non-toxic		—
Benzene hexachloride	1,2,3,4 5,6-Hexachloro-cyclohexane	Moderately toxic	40†	Phenobarbital
Lindane	Gamma isomer of benzene hexachloride	Moderately toxic	15	Phenobarbital
Chlordane	1,2,4,5 6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindane	Moderately toxic	5–60†	Phenobarbital
Toxaphene	Chlorinated camphene, principally polychlorinated bicyclic terpenes (65–67% Cl_2)	Moderately toxic	2–7†	Phenobarbital
Aldrin	1,2,3,4,10,10-Hexachloro-1,4 4a,5,5,8,8a-hexahydro-1,4,5,8-dimethano-naphthalene	Moderately toxic	4	Phenobarbital
Dieldrin	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a octahydro-1,4,5,8-di methanonaphthalene	Moderately toxic	4	Phenobarbital
Parathion	o,o-Diethyl-o-*p*-nitrophenyl-thiophosphate	Highly toxic	0 1†	Atropine
Methyl parathion	o,o-Dimethyl-o-*p*-nitro-phenylthiophosphate	Highly toxic	0 15	Atropine
OMPA	Octamethyl pyrophosphoramide	Highly toxic	0 15	Atropine
"EPN"	Ethyl *p* nitrophenyl-thionobenzenephosphate	Highly toxic	0 15	Atropine
TEPP	Tetraethyl pyrophosphate	Extremely toxic	0 01†	Atropine
HETP	Hexaethyl tetraphosphate	Highly toxic	0 1	Atropine
Piperonyl butoxide	(6-Propylpiperonyl)-butyl-carbityl ether	Practically non toxic		—
"Lethane 384"	b Butoxy b'-thiocyanodiethyl ether	Moderately toxic	7†	—
"Thanite"	*Isobornyl* thiocyanoacetate	Slightly toxic	70	—
"Dilan"	Mixture of propane and butane bases of 2-nitro-1,1 bis(*p*-chlorophenyl)	Slightly toxic Slightly toxic		—
Phenothiazine	Thiodiphenylamine	Practically non-toxic		—
Pyrethrum		Slightly toxic	15–100†	—
Pyrethrins		Slightly toxic		—
Allethrin	Allyl cinerin	Slightly toxic		—

TABLE 65—*Continued*

Preparation		*Comparative toxicity**	*Dangerous oral dose*** (Gm. 62 Kg)	*Antidotes*
Common name	*Chemical name*			
Derris		Slightly toxic	10–100 †	—
Rotenone		Slightly toxic		—
Dihydrorotenone		Slightly toxic		—
Tobacco		Moderately toxic	30 †	—
Nicotine		Extremely toxic	0 06 †	—
		RODENTICIDES		
Barium carbonate		Moderately high	3 9 †	Magnesium sulfate
Thallium sulfate		Highly toxic	1 0 †	—
Strychnine sulfate		Highly toxic	0 1 †	—
ANTU	1-(1 Naphthyl) 2 thiourea	Slightly toxic		—
1080	Sodium fluoroacetate	Highly toxic	0 15 †	Glyceryl monoacetate
Warfarin	3 (α Acetonylbenzyl) 4 hydroxycoumarin	Slightly in single doses (highly toxic in frequent successive doses)	0 5	Vitamin K, whole blood
Castrix	2 Chloro 4 dimethyl amino 6-methyl pyrimidine	Extremely toxic	0 05 †	Pentobarbital
		HERBICIDES		
Sodium chlorate		Moderately toxic	5 †	Methylene blue
Pentachlorophenol		Moderately toxic	5 5	—
Sodium pentachlorophenate		Moderately toxic	20 0	—
Ammonium sulfamate		Slightly toxic		—
2,4 D	2,4 Dichlorophenoxy acetic acid	Slightly toxic	35	—
Maleic hydrazide		Slightly toxic		
Alpha naphthyl acetic acid		Slightly toxic	70	—
DNP	2,4 Dinitro phenol	Highly toxic	2 5 †	—
DNOC	4 6-Dinitro-*o* cresol	Highly toxic	2 0	—
DN 111	2,4 Dinitro-*o*-cyclohexyl phenol dicyclohexylamine	Moderately toxic	25 0	—
		FUNGICIDES		
Ethyl mercury phosphate		Highly toxic	2	BAL
Phenyl mercuric triethanol ammonium lactate		Highly toxic	2	BAL
Nabam	Disodium ethylene-bis dithiocarbamate	Practically nontoxic		—
341C	Glyoxalidine acetate	Slightly toxic		—
Chloranil	Tetrachloro-*p* benzoquinone	Slightly toxic		—
		MISCELLANEOUS PESTICIDES		
HCN	Hydrogen cyanide	Extremely toxic	0 6 †	Methylene blue, sodium thiosulfate
Dichloroethyl ether		Slightly toxic	100 †	—
Naphthalene		Highly toxic	3 †	Whole blood
DMP	Dimethyl phthalate	Practically non toxic		—

[illegible]

senic and fluorine compounds being the most extensively employed The arsenicals include calcium copper lead magnesium manganese and zinc arsenates arsenic trioxide sodium and zinc arsenites and copper acetoarsenite (Paris green) Fluorine compounds include barium calcium and sodium fluorosilicates sodium fluoroaluminate (cryolite) and sodium fluoride Tartar emetic (antimony potassium tartrate) corrosive sublimate (mercuric chloride) sodium borate (borax) and the selenium compounds sodium selenate and potassium ammonium seleno-sulfide, have more restricted application These materials are commonly used as dusts aqueous sprays and sometimes in sweetened baits depending on the toxic properties and end use of the chemical involved *Symptoms of poisoning* and recommended treatment for arsenic boron fluorine and mercury compounds are presented in Chapter 50 Antimony strongly resembles arsenic in its effects and the various measures including dimercaprol U S P (BAL) recommended for arsenic intoxication are applicable to poisoning from antimony containing insecticides

Selenium

Metallic selenium is virtually nontoxic because of its insolubility The more soluble salts are highly toxic and may be absorbed *through the respiratory* and digestive tracts Gastrointestinal disturbances eye nose and throat irritations severe dermatitis porphyrinuria and enlarged livers have been observed in persons exposed to toxic amounts of selenium from industrial processes or who lived in seleniferous areas Treatment is largely symptomatic and supportive High protein diet and the addition of sodium arsenate (5 to 10 p p m) to drinking water counteracted the symptoms of chronic poisoning in experimental animals It has been reported that the ingestion of 1 Gm bromobenzene increased the urinary excretion of selenium and allayed the skin conditions in human *poisoning*

Sulfur is a relatively inactive substance however, large doses can be poisonous Deaths due to sulfur poisoning have been recorded in livestock and pets

SYNTHETIC ORGANIC INSECTICIDES

Synthetic organic insecticides are more diversified Five major groups of organic compounds constitute this subdivision chlorinated hydrocarbon, dinitrophenol organic phosphorus piperonyl and thiocyanate compounds

Chlorinated Hydrocarbon Compounds

The chlorinated hydrocarbons such as aldrin benzene hexachloride, chlordane *DDD (dichlorodiphenyldichloroethane)* DDT (dichlorodiphenyltrichloroethane) dieldrin lindane methoxychlor and toxaphene are noted for their residual properties or persistence even after single applications They are toxic to humans and other forms of animal life but less so than the organic phosphorous compounds Their capacity to produce injury varies with the compound the type of exposure, the formulation and method of application the frequency, amount and duration of contact and other circumstances of use Poisoning may occur both from single exposure to appreciable amounts of the agent and from frequent successive exposures to small quantities The use of solvents and wetting agents in the formulation or use of finely dispersed preparations and the presence of *oil or grease on the skin facilitate* absorption of the products into the body Application under confined conditions such as in an unventilated room or without suitable protective equipment when handling the products for prolonged periods or in concentrated form also reduce the safety with which the chlorinated hydrocarbon insecticides may be employed

Symptoms The symptoms of acute poisoning from the chlorinated hydrocarbon insecticides follow a common pattern referable to the central nervous system Salivation nausea and vomiting irritability muscle spasms incoordination convulsions collapse, and death have been reported The predominance of any particular symptom or group of symptoms varies with individual compounds and the severity of poisoning

Twitching of the eyelids is an early sign of poisoning which has been observed in animals This can be followed by tremors which begin in the muscles of the head and neck and eventually involve the entire musculature being most pronounced in the extremities

Hyperexcitability nervousness restlessness micturition as well as muscle spasms and lack of coordination may also be among the first signs of intoxication These may be preceded by salivation nausea and vomiting if the material has been ingested Muscle spasms may then follow which increase in frequency and intensity and culminate in convulsions The convulsive seizures in poisoning by compounds of this class are similar to those encountered in picrotoxin poisoning Generalized epileptiform convulsions are the most prominent features in toxaphene poisoning Convulsions of a tonic and clonic nature are characteristic of poisoning by aldrin dieldrin benzene hexachloride or its gamma isomer lindane Aldrin and dieldrin convulsions may or may not be separated by observable periods of depression and death can occur both during convulsions or during periods of depression The immediate cause of death in most instances is respiratory failure although death may be caused by ventricular fibrillation Many chlorinated hydrocarbons sensitize the heart to the extent that small doses of epinephrine induce ventricular fibrillation

Symptoms of chronic poisoning by the chlorinated hydrocarbon insecticides have a similar common relationship Loss of appetite and weight emaciation hyperirritability tremors convulsions, coma and death have been observed in experimental animals Occasional instances of blood abnormalities from human exposure to formulations of DDT and certain other compounds in this class have been reported These manifestations are probably attributable to impurities or solvents present in the formulation Albuminuria which developed shortly before death was in some instances the only laboratory evidence of cumulative poisoning Headache general malaise accompanied by sudden and unexplained loss of appetite and weight are other nonspecific signs of cumulative effects In all cases however the severity of the symptoms is dependent upon the frequency and level of exposure to the particular chemical

Treatment The treatment of poisoning from chlorinated hydrocarbon insecticides is symptomatic It is directed towards removing the toxicant from the skin or alimentary tract controlling any irritant skin conditions and counteracting the neurologic symptoms and other manifestations of systemic poisoning Prompt removal of the material from the gastrointestinal tract by lavage saline cathartics and immediate washing of the skin after contact should be done to prevent or reduce absorption Milk oily purgatives and other fatty or oily demulcents or evacuants should be avoided because of their capacity to increase absorption of the toxicants Dermatologic therapy should be employed for the management of inflammatory or other irritant skin conditions If tremors or convulsions develop, 0 1–0 3 Gm phenobarbital sodium should be administered Where immediate effects are desired such as the control of violent convulsive seizures pentobarbital sodium or other short acting barbiturates may be used in comparable

and fungicidal properties It is a primary irritant and photosensitizing agent In the form of a fine insecticidal dust or as vapors produced in the drying of medicinal forms of the chemical, it has caused severe irritation of the skin nasal and bronchial passages and inflammation *of the eyes Its* internal use in humans as an anthelminthic and urinary antiseptic has been discouraged because of reports of liver damage and hemolytic anemia In the insecticidal concentrations commonly used these systemic effects are not likely to occur Treatment is directed towards removal of the irritant from the environment and dermatologic therapy as indicated

BOTANICAL INSECTICIDES

Derris (Rotenone)

The insecticidal properties of plants belonging to the genera *Derris* and *Lonchocarpus* (cube timbo) are due to a number of toxic principles including rotenone and the rotenoids, deguelin tephrosin and toxicarol which are chemically and biologically similar to rotenone The rotenoids are less insecticidal but more toxic to humans than rotenone and partially contribute to the greater toxicity of some samples of the crude drug over its principal insecticidal component The ground roots and extracts of the roots of rotenone bearing plants are used as insecticides They *are prepared for use as dusts with inert* diluents or with other insecticides as washes and dips against animal ectoparasites, as agricultural horticultural and household sprays as emulsions lotions and ointments for treatment of head lice scabies, and as a palliative for chigger bites

Symptoms Local effects reported following exposure to derris include con*junctivitis, dermatitis, pharyngitis* and rhinitis In the finely divided form it has been found to be irritating to the skin of experimental animals, especially where two skin areas are in contact In the undiluted form it was also found to be irritating to the conjunctiva and, in man, produced a numbness of the mucosa of the nose and throat of several hours duration Orally, *it is a gastrointestinal irritant and produces* nausea and vomiting promptly after ingestion This, coupled with its stimulant action on the emetic center after absorption, tends to force expulsion of the material before serious poisoning occurs Oils and fatty foods facilitate absorption of the material The size of the particles of derris also influence toxicity, those in a finely divided condition being several times more toxic In the case of inhalation toxicity, however, the toxicity is believed to be increased several hundred times over oral toxicity as determined by intravenous administration which can be a close measure of inhalation toxicity Although the toxicity of derris is not entirely dependent on its rotenone content, the effects are largely the same This is also true of derrid the active resin in derris which contains an impure form of rotenone and the hydrogenated derivative, dihydrorotenone

Treatment Treatment is largely symptomatic and supportive If the material contacts the eye, irrigation with isotonic sodium chloride solution is indicated If a dermatitis is present the involved area should be cleansed with starch solutions *wet dressings of aluminum* subacetate or potassium permanganate solutions applied and together with a protectant such as zinc oxide ointment U S P or Lassar s plain zinc paste U S P The irritant and emetic actions of derris or its constituents predispose to removal of much of the ingested material Gastric lavage and a saline cathartic may be used if desired Oily cathartics and morphine should be avoided, and the patient placed on low fat diet until symptoms subside

Pyrethrum (Pyrethrins)

Pyrethrum is one of the oldest insecticides known to man It is prepared for use in aerosols, dusts, sprays, and ointments The ground flowers are used undiluted or mixed with inert diluents or other insecticides for use as household and horticultural dusts Liquid extracts or suspensions employing kerosene, pine oil or other hydrocarbon solvents and wetting agents such as soap are used in preparing agricultural live stock, and household sprays

The constituents of pyrethrum that are active as insecticides are the four esters pyrethrins I and II and cinerin I and II An ill defined fraction containing resins camphors, and essential oils is thought to be mainly responsible for the skin irritant properties of pyrethrum while an allergen which is probably a pollen causes asthma and other allergic reactions in sensitive per sons The allergenic substance in pyreth rum is believed to be closely related to ragweed pollen since there is a high fre quency of cutaneous reactions to pyrethrum in ragweed sensitive individuals

Symptoms Pyrethrins are acrid bitter tasting substances which can induce numb ness of the lips and tongue They are slightly sternutatory and without irritating effects on the skin, however contact with the conjunctiva will produce chemosis In traperitoneal injection into laboratory animals produces increased respiration hyperexcitability, incoordination, tremors paralysis and death due to respiratory fail ure They are considerably less toxic orally Vertigo has been experienced by workers handling large quantities of pyrethrins

Pyrethrum dust may produce allergic attacks in persons sensitive to ragweed pollen It has been reported as an etiologic factor in asthma and vasomotor rhinitis Dermatitis is most frequently encountered in factories where the powder is ground The lesions are usually of a mild nature and quickly disappear under ordinary treatment. Several severe and fatal cases of poisoning due to the inhalation or inges tion of the undiluted powder have also been recorded The symptoms of poisoning in the human cases were substantially the same as those observed in experimental animals poisoned by pyrethrins

Treatment Treatment consists of re moval of the offending agent from the en vironment and supportive therapy for the asthmatic or dermatologic condition which may be present

Tobacco (Nicotine)

Tobacco has long been used as a botan ical insecticide in the form of powders and aqueous extracts It is still employed com mercially against poultry lice in the powdered form although nicotine, its most important insecticidal principle, is the more widely employed material Nicotine is a volatile colorless and odorless liquid which turns yellow to brown on exposure to air and light It is available as the free alkaloid as water dispersible and soluble salts of inorganic and organic acids and as nicotine sulfate complexes with bentonite or peat For these purposes it is used in the form of aerosols, dusts, paints and sprays against fruit It has no accepted hu man therapeutic use but it is employed in veterinary medicine as an anthelminthic, dip and ointment for the control of animal parasites Anabasine an isomer of nicotine has attracted attention in this country and is used abroad because of similar insecti cidal properties

Symptoms Tobacco is a strong local irritant causing violent sneezing and irrita tion of the oral mucosa If ingested it produces nausea and vomiting, profuse perspiration and muscular weakness es pecially in non smokers These and more severe physiologic effects are due to nico tine

Nicotine is a powerful and rapidly acting

Symptoms Sodium fluoroacetate acts *predominantly on the heart and the central* nervous system In one case of nonfatal poisoning in which some of the powdered material was inhaled the following symptoms were reported immediate tingling sensation of the nasal passages and around the corners of the mouth followed by tingling of the arms and legs and numbness of the entire face Spasmodic contractions of the voluntary muscles and gradual loss of speech were next noted Unconsciousness occurred two and a half hours after the accident

Symptoms recorded following the ingestion of this poison included excessive salivation nausea and vomiting muscular twitchings cardiac irregularities cutaneous hyperesthesia stertorous breathing cyanosis generalized convulsions and death from ventricular fibrillation or respiratory failure Symptoms frequently appear soon after ingestion but may be delayed for several hours They usually last for twelve to twenty four hours although reports of their persistence for several days or more are available

Treatment There is little evidence for the effectiveness of any treatment measure for the management of sodium fluoroacetate poisoning in man Contaminated eyes or skin should be immediately flushed to remove the poison Gastric lavage should also be promptly undertaken if the material has been ingested Emetics and saline cathartics may be of additional value in its elimination The oral administration of 50 per cent ethyl alcohol and 5 per cent acetic acid alone or in combination at doses of 4 cc per kg body weight every three or four hours has been proposed because of their protective action in experimental animals Monoacetin (glyceryl monoacetate) is also effective in animals and is recommended in doses of 0 25 cc per kg body weight intramuscularly every hour if available

For the control of convulsions, repeated small intravenous doses of a short acting barbiturate (such as amobarbital sodium) may be required Considerable care must be taken to guard against excessive depression which may result from the potentiating effects of sodium fluoroacetate with barbiturates Intravenous plasma 5 cc per kg body weight, is also of value Larger doses should be avoided because of the danger of further impairing cardiac function Slow intravenous injection of 1 Gm of procaine amide hydrochloride has been recommended as a measure to restore normal rhythm in ventricular fibrillation

Warfarin

Warfarin is a multiple-dose rodenticide which is related to the anticoagulant drug dicumarol It is an odorless tasteless water insoluble compound which produces a reversible and controllable hypoprothrombinemia and capillary injury The powdered concentrate containing 0 5 per cent warfarin is available in inert diluents such as corn starch A warning dye may be added to give the concentrate a slightly greenish tint in order to distinguish it from food It is used at levels of 0 025 per cent to 0 010 per cent in baits for the control of rats and mice The occupational risks in the handling of warfarin concentrates and baits are comparatively slight if ordinary precautions are taken

Symptoms *In single large doses* warfarin does not produce obvious signs of poisoning in experimental animals but in successive *small daily doses cumulative* effects appear in three or four days These include weakness pallor subcutaneous *hemorrhages oral or rectal bleeding* weight loss without appreciable loss of appetite and death after twelve to fifteen days The only known human case of poisoning presented a generally comparable set of symptoms In this instance the individual purposely consumed with suicidal intent

four ounces of the powdered concentrate over a four day period A general feeling of weakness was experienced during the next two days A slight bloody tinge to the urine was also noted On the evening of the third day following discontinuance of the poison abdominal and back pains were felt These continued over to the following day when the patient vomited once Hemorrhage from the nose occurred intermittently during the day and the abdominal pain persisted At this time the patient reported to a doctor and treatment was initiated with prompt response

The treatment of warfarin poisoning is the same as that used in the control of the clinical effects of bishydroxycoumarin (dicumarol ') Transfusions of whole blood accompanied by the slow intravenous administration of massive doses of a water soluble form of vitamin K (such as menadione sodium bisulfite 50–100 mg) are recommended until the prothrombin time is restored to normal

Herbicides

WEED CONTROL chemicals are of two broad types general contact weed killers and selective herbicides Common chemicals used as contact weed eradicators are sodium chlorate sodium arsenite sodium hydroxide sulfuric acid and petroleum products such as diesel oil crude oil and stoddard solvent These materials are comparatively inexpensive but are dangerous to humans and animals The dangers from petroleum products however are much less than those from the other substances listed The toxic properties of these materials and the recommended treatments for poisoning are similar to compounds presented in the preceding chapter

Organic compounds other than petroleum products include salts of pentachlorophenol and trichloracetic acid dinitro phenols and ammonium sulfamate With the exception of the last named compound all are toxic chemicals The selective herbicides or hormone type weed killers are plant growth regulants and as a group are relatively nontoxic They include α naphthaleneacetic acid maleic hydrazide chlorinated phenoxyacetic acid derivatives (2 4 D & 2 4 5 T) and *o* isopropyl *n* phenyl carbamate (IPC) Individual sensitivity to the phenolic type of compounds may be experienced by persons sensitive to phenols otherwise they are nonirritating to the skin except in concentrated form although the dusts are irritating to the eyes and respiratory tract The petroleum products used in certain formulations are often a cause of complaint Gastrointestinal irritation is the most likely symptom to be encountered after ingestion of large amounts of these compounds Treatment should be directed towards removal of the compound from the skin or stomach and alleviating such other symptoms as may arise

Pentachlorophenol

Pentachlorophenol in a 5 per cent solution in oil is used as a wood preservative for protection against termites powder post beetles and fungi It is a substance which possesses considerable toxicity and is absorbed from the skin gastrointestinal tract, and probably from the respiratory tract A powerful skin irritant it produces dryness wrinkling and temporary loss of hair in the area affected When heated its vapors are pungent and highly irritating to the eyes and respiratory passages On ingestion it is an irritant and convulsant poison

eucalyptus, and cedar which were used alone or in combination with spirit of camphor and a suitable base They gave variable protection, were often irritating to the eyes and sometimes to the skin and in general, were cosmetically unacceptable to most users A number of synthetic substances have been introduced which are superior when applied to the skin or impregnated into clothing Dimethyl phthalate, *a a* dimethyl *a* carbutoxy *a* pyrone ('Indalone'), 2-ethyl 1, 3 hexanediol ('Rutgers 612'), and dimethyl carbate (dimethyl ester of *cis bicyclo* [2 2 1] 5 *heptene* 2,3-dicarboxylic acid), singly or in combination are considered to be safe as skin repellents for flies biting gnats, and mosquitoes Materials such as *n* butylacetanilide are safe for impregnating clothing but are quite irritating when applied to the skin Other materials such as NMRI 448, a mixture of 2 phenyl and 2 cyclohexyl cyclohexanol are toxicologically unacceptable except under limited skin use Benzyl benzoate is acceptable for topical application for protection against chigger infestations commonly found in the United States

With the exception of benzyl benzoate, these compounds are poisonous if accidentally ingested and all possess the common property of producing local irritation of various parts of the body under certain circumstances With this same exception they also possess solvent properties and should be kept away from plastic articles rayons and certain other types of synthetic fibers, fingernail polish and varnished and painted surfaces They should not be used around tender areas of the body such as mucous membranes, thin skinned areas such as the groin or over abraded skin surfaces In some preparations, organic solvents are used as vehicles and they may induce a burning sensation and irritation comparable to the repellent substances Intense itching burning, skin rash or other irritations are signs requiring discontinuance of the repellent Treatment is in accordance with procedures outlined in the previous chapter for solvent poisoning

Fumigants

MANY highly toxic substances are employed as fumigants These include the cyanides—cyanogen chloride, and hydrogen cyanide, halogen containing compounds—carbon tetrachloride, ethylene dichloride dichloroethyl ether, methyl bromide and ethylene dibromide and the familiar household and soil fumigants—naphthalene and paradichlorobenzene The symptoms and treatment for the cyanides and the volatile halogenated hydrocarbons have been presented in Chapter 50, accordingly attention will be given only to naphthalene and paradichlorobenzene at this point

Naphthalene

Contrary to popular belief in its harmlessness naphthalene is a toxic material It is absorbed through the skin and from the respiratory and gastrointestinal tracts Oils facilitate absorption from the skin and alimentary tract Severe and fatal poisonings from all three avenues of entrance into the body have been reported Headache nausea and vomiting abdominal pain profuse perspiration, burning sensations in the urethra pain in bladder and kidney regions hematuria acute nephritis and jaundice hemolytic anemia optic neu

ritis and other signs of general intoxication have been noted Death has resulted from ingestion of as little as 2 Gm of naphthalene Whole blood transfusions followed by sodium bicarbonate every four hours to prevent crystallization of hemoglobin in the kidneys with consequent anuria have been successfully used in treatment of naphthalene poisoning

Paradichlorobenzene

By comparison with naphthalene, use of paradichlorobenzene has had a more favorable record Prolonged exposures to high concentrations are dangerous although short intermittent exposures are believed to be safe except in those who have a marked susceptibility to paradichlorobenzene and related compounds Transient irritation to the eyes, nose, and throat have been noted in mild cases of poisoning while prolonged exposures to high concentrations such as occurs under confined conditions of use or in certain industrial processes have evoked cataracts and toxic hepatitis in workers When ingested it is a gastrointestinal irritant producing nausea, vomiting, diarrhea, and abdominal pain It may also produce liver and kidney damage Treatment consists of removing the substance from the stomach or external environment and symptomatic measures

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Appendix

NORMAL CLINICAL LABORATORY VALUES

BLOOD Chemical Constituents

	Range
Albumin, serum	4.0–5.2 Gm/100 cc
αAmino acids, serum (ninhydrin method)	3.5–5.5 mg/100 cc
Ammonia, serum	0.15–0.3 mg/100 cc
Amylase, serum (Myers and Killian)	<50 units/100 cc
Ascorbic acid, serum	0.4–1.0 mg/100 cc
Base, total, serum	145–155 mEq/L
Bilirubin total serum	0.1–0.8 mg/100 cc
Direct	0.1–0.2 mg/100 cc
Indirect	0.1–0.6 mg/100 cc
Calcium, serum	9–11 mg/100 cc
	4.5–5.5 mEq/L
Carbon-dioxide combining power serum	50–65 volumes per cent
	21–28 mEq/L
Carbon dioxide content serum	*50–70 volumes per cent*
	21–30 mEq/L
Carotenoids, serum	1–3 units/cc
Chlorides, serum (as Cl)	100–106 mEq/L
	355–376 mg/100 cc
Chlorides, serum (as NaCl)	585–620 mg/100 cc
Cholesterol total serum (Schoenheimer Sperry method)	120–260 mg/100 cc
Cholesterol as esters, serum	80–180 mg/100 cc.
Cholesterol ester fraction of total cholesterol serum	60–75 per cent
Creatine (as creatinine) serum	1–2 mg/100 cc
Creatinine, serum	1–1.5 mg/100 cc
Fat neutral, serum	150–300 mg/100 cc
Fatty acids, serum	380–465 mg/100 cc
Fibrinogen, plasma	0.2–0.4 Gm/100 cc.
Globulins, serum	1.3–2.7 Gm/100 cc
Glucose (fasting), blood	70–110 mg/100 cc
Hemoglobin blood, males	14–18 Gm/100 cc
females	12–16 Gm/100 cc
Icteric index, serum	4–7 units
Iodine, protein bound serum	4–8 μg/100 cc
Iron, serum	80–180 μg/100 cc
Lipase, serum	<2 cc (0.05 N NaOH)

Erythrocytes	4 2–5 5 million/cu mm
Leukocytes	5–10 thousand/cu mm
Platelets	200–500 thousand/cu mm
Reticulocytes	0 5–2 0 per cent red cells/cu mı
Erythrocytes	
Diameter, average	7–5 μ
Fragility	
Maximal resistance	0 32 per cent NaCl
Minimal resistance	0 42 per cent NaCl
Color index	0 9–1 1
Hematocrit	42–50 per cent (volume of cells
Hemoglobin	
Adults, females	12 8–15 2 Gm /100 cc
Adults, males	14–17 Gm /100 cc
Children (varies with age)	10–18 Gm /100 cc
Sedimentation rate	
Cutler, men	2–8
women	2 10
Rourke and Ernstene	<0 4 mm /minute
Westergren	<15 mm /hour
Wintrobe, men	0 9 mm /hour
women	0–20 mm /hour
Volume, blood	7–100 cc /kg body weight 2800–3800 mm /per sq meter bc

BLOOD FUNCTIONAL TESTS

Bromsulfalein	No dye remaining in serum 45 injecting 5 mg per kg bo
Cephalin flocculation	No precipitate
Concentration and dilution	Sp gr of urine after dry da more after water day 1 003
Creatine tolerance	70 per cent ingested creatine adults
Galactose tolerance	Excretion of not more tha galactose in the urine in 5 l ingestion of 40 Gm galacto
Glucose tolerance	Standard After ingestion 10 cose or 1 75 Gm glucose pe weight blood sugar not 180 mg per 100 cc after ½ return to normal in 2 hr present in all urine specim Exton ½ hr blood sugar not 75 mg per 100 cc. highe fasting sugar and 1 hr t

Lipids, total, serum	500–600 mg/100 cc
Magnesium, serum	2–3 mg/100 cc 1 6–2.4 mEq/L.
Nitrogen, nonprotein, serum	15–35 mg/100 cc.
Oxygen capacity, blood	18–22 volumes per cent
Oxygen content, arterial blood	17–21 volumes per cent
Oxygen content, venous blood, arm	10–16 volumes per cent
Oxygen per cent saturation, arterial blood	94–96 volumes per cent
Oxygen per cent saturation, venous blood, arm	60–85 volumes per cent
*p*H serum	7 37–7 45
Phosphatase, acid, serum	
(Gutman or King Armstrong method)	1–4 units/100 cc
(Bodansky method)	0 2–0 8 unit/100 cc
Phosphatase, alkaline, serum	
(Bodansky method)	1–4 units/100 cc
(King Armstrong method)	8–14 units/100 cc
Phospholipids, serum	175–275 mg/100 cc.
Phosphorus, inorganic, serum	3–4 5 mg/100 cc 1–1 5 mM/L
Potassium, serum	4 0–5 0 mEq/L
Proteins, total, serum	6 5–8 0 Gm/100 cc
Prothrombin, plasma (Quick method)	14–18 seconds, depending on thromboplastin used
Sodium, serum	137–143 mEq/L
Sulfates, inorganic serum	0 5–1 5 mg/100 cc
Urea, serum	20–35 mg/100 cc
Urea, nitrogen, serum	*10–25 mg/100 cc*
Uric acid, serum	3 0–6 0 mg/100 cc
Vitamin A, serum	0 4–1 0 I U/cc.

BLOOD CLINICAL EXAMINATIONS

Bleeding time	1–5 minutes
Clot retraction time	1–3 hours
Coagulation time	
Capillary blood	3–6 minutes
Venous blood	5–20 minutes
Formed elements	
Cells, differential count	
Lymphocytes	25–35 per cent (1250–3500 per cu mm)
Monocytes	1–10 per cent (200–1000 per cu mm)
Neutrophils	
Young (nonfilament)	3–15 per cent (150–1500 per cu mm)
Adult (filament)	50–65 per cent (2500–6500 per cu mm)
Eosinophils	0 5–4 per cent (25–400 per cu mm)
Basophils	0 2 per cent (0–200 per cu mm)

Erythrocytes	4 2–5 5 million/cu mm
Leukocytes	5–10 thousand/cu mm
Platelets	200–500 thousand/cu mm
Reticulocytes	0 5–2 0 per cent red cells/cu mm
Erythrocytes	
Diameter, average	7–5 μ
Fragility	
Maximal resistance	0 32 per cent NaCl
Minimal resistance	0 42 per cent NaCl
Color index	0 9–1 1
Hematocrit	42–50 per cent (volume of cells)
Hemoglobin	
Adults, females	12 8–15 2 Gm /100 cc
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Volume, blood	7–100 cc /Kg body weight 2800–3800 mm /per sq meter body surface

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Bromsulfalein	No dye remaining in serum 45 min after injecting 5 mg per Kg body weight
Cephalin flocculation	No precipitate
Concentration and dilution	Sp gr of urine after dry day 1 025 or more after water day 1 003 or less
Creatine tolerance	70 per cent ingested creatine retained in adults
Galactose tolerance	Excretion of not more than 3 0 Gm galactose in the urine in 5 hr after the ingestion of 40 Gm galactose
Glucose tolerance	Standard After ingestion 100 Gm glucose or 1 75 Gm glucose per Kg body weight blood sugar not more than 180 mg per 100 cc after ½ hour and return to normal in 2 hr Sugar not present in all urine specimens Exton ½ hr blood sugar not more than 75 mg per 100 cc higher than the fasting sugar and 1 hr blood sugar not more than 50 mg higher than in the ½ hr specimen

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